ABSTRACTS OF WORLD MEDICINE

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Hygiene and Public Health

1942. **Combined Active and Passive Immunization Against Diphtheria**

A. W. DOWNIE, A. T. GLENNY, H. J. PARISH, E. T. C. SPOONER, R. L. VOLLUM, and G. S. WILSON. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 34–41, March, 1948. 2 refs.

In 1941, Downie *et al.* (*Brit. med. J.*, 1941, **2**, 717) recorded trials of combined active and passive immunization against diphtheria in about 300 university students. The original doses of APT employed were 0·1 and 0·3 ml. with a 4-week interval. At the time of the first injection of APT a dose of 400 to 500 units of antitoxin was injected into the opposite arm. These groups were studied side by side with groups receiving active immunization only. It was concluded that the combined technique as compared with simple active immunization led to some delay, and a slight inhibition, in the formation of antitoxin by the individual. The final degree of immunity did not, however, fall far short of that resulting from active immunization alone (a Schick-conversion rate of 90·9 as against 98%).

The present paper gives an account of a further series of experiments to show the effect of: (1) increasing the dose of APT from 0·1 and 0·3 ml. to 0·3 and 0·3 to 0·5 ml.; (2) reducing the interval between the doses from 4 weeks to 2 weeks; (3) increasing the dose of antitoxin from 500 to 5,000 units. The subjects under test were medical students who had neither had diphtheria nor immunization against the disease. All were bled and Schick-tested before acceptance; only Schick-reactors and those with less than 1/1000 unit of antitoxin per ml. blood serum were retained for further observation. The accepted students were, without selection, divided into two groups. The first group received only active immunization with two doses of APT and the second group APT together with a dose of antitoxin injected into the opposite arm at the time of giving the first dose of APT. Four weeks after the first dose the APT blood was again taken from all the subjects and the second dose of APT was given. Four weeks later there was a third bleeding, and 6 to 8 or 10 to 14 weeks after the second APT injection a final bleeding and Schick test were carried out.

The increased dose of APT appeared to be of little or no benefit to the actively immunized group, but the group receiving the combined immunization responded in a highly suggestive, if not statistically significant, manner. Reducing the interval between the doses of APT from 4 to 2 weeks definitely lowered the antitoxin response of both groups. When the dose of antitoxin was increased from 500 to 5,000 units there was a greater inhibition of antitoxin in the group receiving the larger dose. Even so, with a Schick conversion rate of 97·1% for combined immunization with 500 units of antitoxin the figure for those receiving 5,000 units was no less than 81·5% 12 weeks after the second dose of APT. The authors suggest that in practice the inhibitory effect of the 500 units of antitoxin might be reduced by further increasing both doses of APT to 0·5 ml. and at the same time lengthening the interval between the injections to 6 weeks. [This is an important contribution and these carefully controlled field-observations have yielded results very much in line with those originally obtained in the laboratory. The " blanketing " effect of large doses of antitoxin and the advantage of the wide spacing of APT injections are well demonstrated.] *H. J. Bensted*

1943. **Immunization of Adults Against Diphtheria. With Particular Reference to Dosage and Reactions.** [In English]

I. SCHEIBEL, S. TULINIUS, G. RASCH, K. BOJLEN, and C. B. PETERSEN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 319–350, 1948. 3 figs., bibliography.

In Denmark before the war the ratio of adults to children suffering from diphtheria was 1 : 3. In 1942 a change began and the ratio of adult to child cases in 1942 was 1 : 1·3, in 1943 1·8 : 1, in 1944 2·6 : 1, and in 1945 2·8 : 1. It was only after the occupation of the country by German troops that gravis infections accounted for a considerable proportion of all cases. In 1945 the total diphtheria fatality rate was 10·9%, and in children under 15 years 17%. In 1941 the immunization campaign was intensified and the authors estimate that 90% of children between the ages of 1 and 15 years and 35 to 40% of adults have been immunized; they believe that the change in the morbidity ratio is closely connected with immunization.

The effects of immunization in adults have not been studied so fully as in children, and the present investigation was undertaken to find a method which would reduce the reactions and limit the number of doses. The authors tried to find out whether: (1) the small-dose method would stimulate the production of sufficient antitoxin; (2) the number of injections could be reduced; (3) the dosage could be halved; and (4) the frequency and severity of the complications decreased with the dosage employed. A survey of the distribution of natural antitoxin in 682 persons, 65 of whom had previously had diphtheria, was undertaken. Of those who had had

diphtheria, 61·2% aged from 15 to 29 years did not have measurable quantities of natural antitoxin in their serum; for those aged from 30 to 49 years the corresponding figure was 40·2%. Immunity was no greater among those who had had diphtheria than among others. Immunization tests were carried out with the same batch of alum-precipitated toxoid containing 25 Lf units per ml., the dosage being as follows:

	Dosage	*Interval*
1.	2×1 ml.	4 weeks
2.	2×0·5 ml.	4 weeks
3.	4×0·2 ml.	1 week, 3 weeks, and 1 week
4.	3×0·2 ml.	2 weeks
5.	2×0·2 ml.	4 weeks

The effects of these procedures were measured by antitoxin titrations and the analysis of the results is presented in detail. It was found that after a single injection the antitoxin production depended to some extent on the size of the dose, but although the mean antitoxic value was increased there was no increase in the number of individuals who became immune, as judged by a serum titre of 0·01 unit per ml. Two doses of 0·2 ml. given at a week's interval conferred the same degree of immunity as 1 dose of 1 ml. Two doses of 0·2 ml. at a fortnight's interval conferred greater immunity than did the same doses at a week's interval, but there was no demonstrable difference when the interval was increased from 2 to 4 weeks. When the results were examined after more injections had been given, there appeared to be no dependence of the antibody production on the antigen doses employed. Further, the antitoxin titres 1 year after immunization were independent of the methods employed.

Reactions were influenced by the presence of natural antitoxin, a history of diphtheria, and the dose of prophylactic and age, but not by sex. The authors suggest that in immunizing adults one of two methods should be employed; either 2 doses of 0·5 ml. with an interval of 4 weeks should be followed a year later by another 0·5 ml. or 3 doses of 0·2 ml. at fortnightly intervals followed a year later by 0·2 ml. *J. Smith*

1944. **Immunization of Adults with Diphtheria Toxoid. III. Highly Purified Toxoid as an Immunizing Agent**
A. M. Pappenheimer and H. S. Lawrence. *American Journal of Hygiene* [*Amer. J. Hyg.*] **47**, 241–246, March, 1948. 1 fig., 13 refs.

Among individuals with a positive Schick reaction only a small number were sensitive to a highly purified diphtheria toxoid, whilst all the Schick-positive group reacted to a greater or less extent to the P fraction. The authors therefore recommend the use of purified toxoid for immunization of most Schick-positive adults. As about 30% of the Schick-negative individuals had allergic reactions to the toxoid, diluted to the usual strength for Schick testing, the administration of undiluted toxoid would produce undesirable general reactions in adults, unless preliminary tests were made. In their investigations, the authors found that adults immunized with 3 doses of purified toxoid at 3-week intervals showed no general reaction. The local reactions were not severe. In allergic individuals there is a marked anamnestic response to the injection of very small doses of toxoid. *Franz Heimann*

1945. **Influenza B. Study of a Localized Outbreak Preceding the 1945 Epidemic**
Commission on Acute Respiratory Diseases. *American Journal of Hygiene* [*Amer. J. Hyg.*] **47**, 297–303, May, 1948. 1 fig., 29 refs.

A localized outbreak of influenza B at the army post of Fort Bragg, North Carolina, 2 months before the onset of the 1945 epidemic is reported. A battery made up of 230 recruits was studied from July to October, and serological examinations were made before and after the outbreak in the first and sixteenth weeks of training, a fourfold increase in titre of antibody being taken as evidence of the presence of influenza; the serological methods of examination and their evaluation are described. Fourfold, or greater, increases in titre to influenza virus B were found predominantly after febrile respiratory illness, but their occurrence in an approximately equal number of the individuals who had no such history induced the authors to classify such cases as "inapparent" influenza. The study showed that individuals with lower initial antibody titres were generally the ones who developed febrile respiratory affections with the largest increases in titre. *F. T. H. Wood*

1946. ***Entamoeba histolytica* in Wild Rats Caught in London**
R. A. Neal. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 90–93, March, 1948. 3 figs., 11 refs.

Seven out of 11 wild rats from a particular source in London were found to harbour amoebae possessing all the characters of *Entamoeba histolytica*. The amoebae were restricted to the caecum of the rats but macroscopical lesions were not apparent in the caecal walls. The vegetative forms were typical except that ingested red blood cells were not seen. Only occasional uninucleate and binucleate cysts were found and concentration methods failed to reveal mature forms. Cultures from the wild rats were successfully transferred to series of young laboratory-bred rats by the intracaecal route, and the caecal wall was attacked with varying degrees of severity. Amoebae were readily demonstrated in sections of the ulcers, and smears from the ulcers showed typical vegetative forms containing red blood cells.

The inhabitants of the house in which the rats were caught were Cypriots, some of whom had recently arrived from Cyprus. Two of these individuals were found to be passing abundant cysts of *E. histolytica* in their faeces. Four "clean" rats, comparable in weight to those naturally infected, were inoculated orally with cysts from these carriers and in 2 the response was similar to that in the original wild rats. The caecum contained vegetative forms of *E. histolytica*, but no lesion of the caecal wall was visible. Numbers of rats from other sources were examined but no amoebic infection

was found. There appear to be reasonable grounds for associating the original natural infection of the 7 rats with the 2 human carriers. The place of rats in the epidemiology of human amoebiasis deserves full consideration. *H. J. Bensted*

1947. **Thyroid Enlargement and Other Changes Related to the Mineral Content of Drinking Water (with a note on Goitre Prophylaxis)**
M. M. MURRAY, J. A. RYLE, B. W. SIMPSON, and D. C. WILSON. *Medical Research Council Memorandum*, No. 18, 1–39, 1948. 1 fig., bibliography.

The Board of Education's 1924 clinical survey of thyroid enlargement suggested that physiological goitre differed from endemic goitre only in stage or degree. In the present survey physical measurement of the gland was found to be inadvisable. Accordingly a system of inspection and bimanual palpation of the gland was devised which is described in considerable detail. The subject is examined in good daylight while seated on a swivel stool. The thyroid gland of the child or adolescent is assessed and placed in one of the following four groups: (*a*) invisible at rest; (*b*) visible but soft, smooth, and symmetrical; (*c*) visible +, without asymmetry, firmness, or nodular change (Rossetti neck); (*d*) with pathological degrees of firmness, asymmetry, or nodular change. In five English and two Scottish counties 4,000 school children were surveyed. Most of the children seen fell into Group (*a*) and few into Group (*d*). Adolescent hyperplasia was seen mainly in Groups (*b*) and (*c*). Most of the Group (*b*) glands became less visible or invisible after puberty and so were regarded as normal; some of the Group (*c*) glands, however, seemed to persist for a time and this type was therefore deemed to be outside physiological limits. Enlargement of the gland in early childhood or persistence of the visible gland after the age of 18 years was thought to indicate that the gland might develop abnormally in response to iodine lack and undergo changes which would be more than purely physiological or transitory.

A comparative survey was made of school children in four areas: (1) with a soft water of low iodine content (1·1 μg. per litre) in North Devon; (2) with a hard water of low iodine content (2 μg. per litre) in North Oxon; (3) with a hard water of high iodine content (10·1 μg. per litre) in Berkshire; (4) with a soft water of very high iodine content (50·2 μg. per litre) in Essex. The results are fully tabulated. They show in the areas of low iodine content a high mean incidence of thyroid enlargement with a low ratio of females to males; in many other areas there was a low " residual " incidence of thyroid enlargement with female predominance. Iodine contents of 3 μg. or above per litre are usually associated with low goitre incidence; a clear-cut inverse relation is, however, not always observed and it seems that the hardness of water and other factors must also play a part which is not yet clearly understood. If one may postulate for the United Kingdom a " non-goitrous " iodine content of water, the lowest figures may be 5 μg. per litre for hard waters and 3 μg. per litre for soft waters. Samples of drinking water were taken for analysis from 81 places in England and Wales and from 64 Scottish towns. Forty English and 61 Scottish samples contained less than 3 μg. of iodine per litre. Goitre incidence, however, in Scotland was less than expected, but this might be due to the general softness of Scottish waters. The distribution of goitre in relation to geological formation was also studied with interesting results. It was thought that certain fossil forms in the soil might acccount for the high iodine content of some local water supplies. The relation of iodine intake and absorption to calcium and fluorine is also discussed.

Daily requirements of iodine are assumed to be 100 μg. for adults and 150 μg. for growing children, adolescents, or pregnant women. Thus the chief source of this iodine cannot be the water supply, even though this latter may appear to determine the local incidence of thyroid enlargement. There is much evidence that sea fish is important in protecting against goitre; indeed, sea fish and foods derived therefrom are the only common articles of diet which are rich in iodine. Goitre seems to be more common in those rural areas where sea fish is scarce or dear; considerations of cost also seem to have excluded fresh fish from many school meal menus, even though it is a popular item. Three examples are quoted to illustrate the possible importance of a genetic factor in the endemic goitre problem. An innate liability seems to exist in some persons, whereas others may have a high natural resistance to the action of adverse factors. The quantity of iodine consumed and the duration of any iodine deficiency are clearly of importance to both types of person.

Other effects of iodine deficiency investigated include: (1) Cretinism. Records were obtained of cretins in four counties. Two families each having two cretins were investigated and both were found to contain in addition females with goitres. (2) Deaf-mutism. Incidence of this condition is relatively high where endemic goitre prevails. Some deaf-mutes have large thyroids while others, not themselves goitrous, have relatives thus affeeted.

The use of salt containing 1 part of potassium iodide per 100,000 parts of sodium chloride should be convenient and effective as a prophylactic against goitre in Great Britain. An average daily salt intake of 10 g. per head should thus yield 0·1 mg. of iodide or 76 μg. of iodine. No ill effects are to be expected and the extra retail cost will be not more than fourpence per head annually. Vitamin A and D tablets issued for the use of expectant mothers have since 1947 been fortified by adding enough potassium iodide to provide 100 μg. of iodine in each tablet. One tablet is an average daily vitamin supplement. *D. Livingstone*

1948. **Principles of Standardization of an Artificial " Micro-climate ".** (Принципы нормирования производственного микроклимата)
G. K. SHAKHBAZYAN and N. K. VITTE. Гигиена и Санитария [*Gigiena*] No. 3, 22–29, 1948. 4 figs.

The ideal climatic conditions vary with the work being done. Thus the heat balance was maintained during light work with an external temperature of 25° C.,

but for heavy work 10° C was ideal, and for extremely heavy work the freezing point was most suitable. It is pointed out that a " climate " undergoes variations under many headings, and that physical output decreases with rising temperature, at least above a certain point. Corresponding with the rise in temperature is an increase in pulse rate and greater fatigue with lesser efficiency of the heart. [The article is a review of factors already well known.] *G. C. Pether*

1949. **Bacterial Contamination of the Air in Living Quarters with Various Densities of Population.** (Бактериальное загрязнение воздуха в жилых помещениях с различной плотностью заселения)
F. S. Epstein and E. G. Salamandra. Гигиена и Санитария [*Gigiena*] No. 3, 14–22, 1948. 3 figs.

Experiments were made to determine the aerial content of streptococci and the variations occurring with increase and decrease of living space per person, the season of the year, and other factors. When each person occupied from 2·5 to 3·6 sq. metres 468 colonies were counted on a medium, whereas when living space increased to from 10 to 18 sq. metres the number of culture colonies fell to 86. Two seasonal rises were observed, one in about April and the other in about October. These would coincide in Russia with a fairly rapid change in temperature and living conditions. When accommodation had improved, so that each person had his own room, there was a fairly sudden fall in the colony counts. It is thought that the figures obtained justify further work on the value of aerosols, particularly since the bacterial counts rose considerably when any illness of the nose and throat or respiratory tract affected the persons under observation. *G. C. Pether*

1950. **Further Work on Forecasting Smallpox Epidemics in India and British Tropical Countries Based on Previous Climatic Data**
L. Rogers. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 19–33, March, 1948. 5 figs., 12 refs.

The author recorded in 1926 a study of smallpox data for 60 years in India in relation to climate, pointing to the strong restraining influence on the spread of the disease exercised by the high absolute humidity caused by the annual high south-west monsoon. Subsequent researches have been more detailed and have been extended to other colonial medical reports: these are described in the present paper. The epidemics of smallpox in India during 50 years were examined and only 5 instances were discovered where low monsoon rain and humidity were not followed by increases of smallpox to epidemic levels; even in these cases there was a material rise in smallpox. The possibility of this relationship holding good in other tropical countries with well-marked dry and wet seasons was studied: in Jamaica there was the same association of high rainfall and absolute humidity with the annual decline of smallpox and vice versa, and on the other hand also there was no such close relationship with either the relative humidity or the mean temperature. Uganda, with no definite dry and wet seasons, has likewise no annual decline in smallpox incidence to a low minimum. Nyasaland, in the southern hemisphere, was seen to have the seasonal increase of smallpox completely reversed, absolute humidity being low in the dry cold months: a rise in the smallpox incidence followed. Bacteriological confirmation of these findings is forthcoming in the work of Downie and Dumbell (*Lancet*, 1947, **1**, 550) on the longer survival of variola virus in dry exudates kept in the dark at room temperature, conditions exactly opposite to those which hinder the spread of infection in India. The author suggests that other airborne diseases in countries with suitable climatic conditions are worthy of study on similar lines. *F. T. H. Wood*

INDUSTRIAL MEDICINE

1951. **Brucellosis in Industry**
C. F. Jordan. *Industrial Medicine* [*Industr. Med.*] **17**, 176–180, May, 1948.

The incidence of *Brucella* infections in all the 48 States of the U.S.A. has been analysed. The number of reported cases for the years 1930–9 averaged 1·99 per 100,000 of population; between 1940 and 1946 this figure rose to 3·11. North Carolina, the only state attempting to eradicate brucellosis from dairy herds, had figures of 0·4 and 0·3 respectively. Vermont and Iowa had rates over five times the average. The infection was studied particularly in Iowa and here the rate more than doubled in 1947; in 25% of the reported cases there was no direct contact with farm animals, and the sex incidence was equal. In the remainder there had been contact, and 88% of this group were men; three-quarters of them were between 20 and 49 years old. Of 2,031 patients reported in 1940–7 from Iowa, 95% were either farm workers or meat packing house employees, but if the estimated population at risk in the various occupations is taken into account, the risk for veterinary surgeons is twice that for packing house employees, over 9 times that for farm hands, and 70 times that for town dwellers in general. Farm hands probably become infected through the skin when handling struggling animals. Active and latent *Brucella* infection has been found in earlier surveys to be present in 18·2% of meat packers. The criterion was an agglutination titre of 1 in 40 or higher. Pigs' blood had a positive titre of 1 in 80 or higher in 3% of the animals tested. In the packing houses most of the men affected with brucellosis were on the killing floors or engaged in meat trimming. *Br. abortus* accounted for 30% of the infections in Iowa between 1927 and 1947; 58% were due to *Br. suis*, and 11% to *Br. melitensis*. The latter seems to be caught from pigs, not goats. Blood cultures are recommended when industrial workers develop fevers; serological tests are next in importance, but skin tests may be confusing. The preventive measures suggested include regular serological tests to detect early or subclinical cases, rubber gloves for those who handle viscera, care of minor injuries, cleansing of packing premises, and control of brucellosis in animals. *J. N. Agate*

1952. **The Effect of the Use of Calcined Alumina in China Biscuit Placing on the Health of the Workmen. A Field Study in a Group of Pottery Workers in North Staffordshire**
A. MEIKLEJOHN and W. W. JONES. *Journal of Industrial Hygiene and Toxicology* [*J. industr. Hyg.*] **30**, 160–165, May, 1948. 8 refs.

Until 1925 fine-powdered flint was used for " placing " china ware for the purpose of biscuit firing. Since then calcined alumina (corundum) has been gradually substituted for the flint, and its use is now established throughout the industry in England. Potters' rot or potters' asthma was very common among china biscuit placers, and under the British silicosis scheme men using flint were (after 1931) required to be medically examined every 18 months. When alumina was substituted the examinations were discontinued. In the present inquiry 52 china-biscuit placers who had previously been examined by the Silicosis Medical Board were re-examined. All of them had been exposed for a considerable time to flint, followed by exposure to alumina for 2 to 16 years. The workmen were convinced that alumina produced a dustier atmosphere than flint, but it did not, like flint, irritate the nose and throat, or induce a feeling of stuffiness on the chest, and the men no longer feared the effects of the dust. They appeared much healthier than the old-time flint placers, though complaints of cough, expectoration, and dyspnoea were as frequent as before. An *x*-ray examination indicated that in 6 of the men there was definite progression of the disease, this being no better than would have been expected if the men had continued to work with flint. However, no evidence was obtained that the alumina was responsible for the adverse effect, and this conclusion was supported by the opinion of the Medical Board. In 1937 they examined 50 men employed in the manufacture of aluminium from alumina and concluded that " there is no evidence of pneumoconiosis or of any other pulmonary disease arising from the considerable dust risk (alumina) to which these men have been exposed ". In 1946 44 of these workmen were alive and well and still at their jobs; the remaining 6 men had died from causes unrelated to pulmonary disease.

H. M. Vernon

1953. **Hair Loss in Neoprene Manufacture**
W. L. RITTER and A. S. CARTER. *Journal of Industrial Hygiene and Toxicology* [*J. industr. Hyg.*] **30**, 192–195, May, 1948. 2 refs.

Loss of hair has been noticed among employees engaged in manufacturing one of the synthetic rubbers, and the authors have attempted to isolate the substances responsible for the loss. Synthetic rubbers are products obtained by the polymerization of certain unsaturated compounds. Neoprene is the generic name of the class of elastomers produced by the polymerization of 2-chlorobutadiene ($H_2C{=}CCl{-}CH{=}CH_2$). This substance—a colourless liquid—is formed from acetylene and hydrochloric acid by a series of reactions. Because of the hazardous nature of the reactions they are carried out in a closed system. Chlorobutadiene is polymerized after initiation by means of typical catalysts of the persalt type, a sulphur-containing compound of the thiuram type being added. The polymeric chlorobutadiene emulsion is then coagulated by freezing on the surface of a brine-chilled drum.

When commercial polymerization of chlorobutadiene was undertaken in an aqueous emulsion some of the employees began to lose their hair after a few weeks or months. The loss of hair could be much reduced by frequent and complete change of the air of the working environment. The hair loss was predominantly on the scalp, and hair always grew again when the employees were transferred to other occupations. Microscopical examination of the hair showed that it came out at the root, a bulb being present at one end of each hair shaft, but there was no evidence of change in the shaft itself. A composite product containing various cyclic and short-chain polymers of chlorobutadiene was prepared; when two drops of this was placed on the back of a mouse or guinea-pig the area covered by the solution became completely denuded of hair in 4 to 10 days. In about 3 weeks hair was again visible over the denuded area, and in 6 weeks it had completely regrown. *H. M. Vernon*

1954. **Results of Influenza Vaccination in Industry During the 1947 Epidemic**
A. M. BAETJER. *Industrial Medicine* [*Industr. Med.*] **17**, 171–175, May, 1948. 7 refs.

An influenza A and B vaccine was given in certain factories during the winter of 1946–7. The expected epidemic in 1947 yielded a low incidence of cases, and these were mild. The responsible virus was influenza A, but the strains were antigenically different from those in the vaccine. Thirteen industrial companies scattered widely throughout the United States were able to supply records for the comparison of vaccinated and non-vaccinated groups. A warning is given of the difficulty of verifying a diagnosis of influenza, and of the bias caused by the fact that those who know that they are susceptible more readily accept voluntary vaccination. It is also difficult to choose groups similar in age and sex distribution. In these 13 companies about 37,000 people were vaccinated and 40,000 not vaccinated. In 7 of them there was no real difference between the incidence of influenza in the vaccinated and in the controls. A lower rate in the vaccinated group was reported by 6 companies, but for various reasons this was not thought to be due to the vaccine. Immediate reactions to the vaccine were reported, but the percentage of employees who lost time was very small. The author suggests that the results are inconclusive because the sickness records provided were inadequate, the epidemic was mild, and there were antigenic differences between the epidemic virus and the viruses of the vaccine. Similar results to these had been reported from a university group and from establishments of the U.S. Army. They do not necessarily mean that influenza vaccination will be of no value in future epidemics. *J. N. Agate*

For Industrial Toxicology, see Section Pharmacology, Abstracts 2025–32.

Anatomy

1955. **Innervation of the Smallest Blood Vessels**
F. A. NELEMANS. *American Journal of Anatomy* [*Amer. J. Anat.*] **83**, 43–66, July, 1948. 14 figs., 21 refs.

The innervation of small blood vessels in the tongue of the living frog was studied by an intravenous methylene blue technique. The frog was pithed, the tongue stretched out under saline and 0·2 to 0·5 ml. of a methylene blue solution (1% methylene blue, 5 ml., 10% sodium pyruvate, 1 ml., 10% sodium tartrate, 1 ml., 0·6% saline, 3 ml.) was injected slowly into the vena dorsalis pedis. The fine nerve fibres in the tongue became visible within 5 to 10 minutes. In some cases good results also were obtained, even in the absence of an active circulation, by injecting about 10 ml. of the solution under pressure into frogs anaesthetized with chloral hydrate.

Non-myelinated nerve fibres were constantly seen along arteriolar-venular (a–v) bridges. Usually at least two fibres with frequent anastomoses were seen. These were continuous with the nerve plexus around the arteriolar system but as a rule most fibres originated from separate long non-myelinated nerve strands from the peripheral branches of the hypoglossal and glossopharyngeal nerves. These strands formed a network of wide mesh, and nucleated broadenings appeared fairly regularly at points of branching. These plasmodial strands and the fibres along arterioles, a–v bridges, and venules formed an apparently syncytial plexus between the smaller branches of the peripheral nerves on one side and the nerve plexus around the larger blood vessels on the other. As a rule no nerve fibres were found around true capillaries, but occasionally fine beaded fibres from the nerve plexus around the a–v bridge ran for a short distance along capillaries which originated from the latter. Owing to the difficulty in identifying true capillaries it could not be stated with absolute certainty that the latter were never supplied by nerves, but such a nerve supply if it occurs must be relatively rare.

In an attempt to study the origin of the plasmodial network the main nerves of the tongue were severed. Degeneration of the nerve trunks was not accompanied by degeneration in the network. Even after many weeks no obvious degeneration was found. It thus appeared that the network did not actually arise from the peripheral nerves. So far as could be seen cervical sympathectomy did not result in degeneration of the network. Combined sympathectomy and section of peripheral nerves was followed after 20 days by increased difficulty in staining, but no gross degenerative changes were seen. No peripheral ganglion cells were found in serial sections of the tongue and it is suggested that the plasmodial network is itself composed of small nerve cells. [No definite proof appears to exist that the plasmodial network is in fact composed of nervous tissue.]

R. Barer

1956. **The Chemical Histology of the Human Placenta and Decidua with Reference to Mucopolysaccharides, Glycogen, Lipids, and Acid Phosphatase**
G. B. WISLOCKI and E. W. DEMPSEY. *American Journal of Anatomy* [*Amer. J. Anat.*] **83**, 1–41, July, 1948. 25 figs., 39 refs.

The histochemical reactions of the placenta and decidua were studied on material from 9 human uteri obtained by hysterectomy between the eighth and sixteenth weeks of pregnancy. Metachromasia was investigated, material being fixed in 4% basic lead acetate and stained with 0·5% aqueous toluidin blue. The trophoblast showed faint and inconstant metachromasia, which disappeared after treatment with ribonuclease, and was therefore attributed to the presence of ribonucleoprotein. The metachromasia in Wharton's jelly, the coats of the umbilical vessels, the stroma of the placental surface, and the walls of the larger placental vessels was intense and constant, and uninfluenced by ribonuclease. It was thought to be due to mucopolysaccharides. Metachromasia was also observed in the ghosts of degenerated placental villi and in the basement membrane at the line of junction of the stroma of the villi with the cytotrophoblast. This was also unaffected by ribonuclease. In the wall of the uterus, metachromasia was found in the matrix and some cells of the decidua, in the uterine secretion, and in the walls of the endometrial spiral arteries. With the exception of the decidual cells, metachromasia in these sites was only a little affected by ribonuclease.

The Bauer technique was used to demonstrate glycogen and some mucopolysaccharides. The former could be removed by digestion in saliva. Glycogen was found in the cytotrophoblast, in the mesenchyme cells of the umbilical cord, and in the stroma cells of the placental villi, as well as in smooth muscle cells. It was very abundant in the epithelial lining of the endometrial glands and in many decidual cells. Bauer-positive saliva-insoluble material was found in the secretion of the endometrial glands. The McManus periodic acid method was used to stain collagenous reticulum, fibrin and fibrinoid, glycogen, and mucus. The secretion of the endometrial glands stained intensely by this method. The cytoplasm of the glandular epithelium was also stained. The distribution of lipids was studied by means of Sudan black staining, and also by the polarising microscope. Birefringent sudanophil droplets were found in the placental syncytium, but not in the cytotrophoblast. Non-birefringent lipids were found in the epithelium of the uterine glands and in the decidual cells. Acid glycerophosphatase was demonstrated by incubating sections with sodium glycerophosphate. The enzyme was found in the syncytium, but was scanty in the cytotrophoblast. The epithelium of the uterine glands was intensely stained by this method. *R. Barer*

Physiology and Biochemistry

1957. **Observations of Arterial Oxygen Content in Children during Inhalation of Air and 100 per cent Oxygen**
S. N. PRESTON and N. K. ORDWAY. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 696–702, March, 1948. 17 refs.

The authors obtained blood samples by femoral puncture from normal children and compared the oxygen tensions after inhalation of air and 100% oxygen, estimating the tensions by a modified Roughton–Scholander technique. The average arterial saturation with the subject at rest and breathing air was 93·1% (limits 91·5 and 95·3%); the average amount of oxygen in physical solution during inhalation of the pure gas was 1·09%, or 55% of the calculated value. A comparable discrepancy exists in figures obtained during air inhalation, and the authors discuss the significance of the difference. *Alex. Comfort*

1958. **Ovarian Response in the Albino Rat to Injected Colloidal Substances**
R. N. BAILLIF. *American Journal of Anatomy* [*Amer. J. Anat.*] **83**, 109–141, July, 1948. 12 figs., 35 refs.

Into 42 albino rats 5 to 7 months old acid colloids were repeatedly injected and the ovarian responses observed. The substances used were: (1) " Erie black " (" chlorazol black E ", a sulphonated acid-azo compound) and (2) colloidal mercuric sulphide. Daily intraperitoneal injections of 1 ml. of a 1% solution were given at first until toxic symptoms appeared; the dose was then halved. The animals were killed after periods of 1 to 7 weeks.

Vaginal smears from animals undergoing injection indicated some disorder of the oestrus cycle, arrest in di-oestrus being very common. This effect was believed to be systemic, and not due to a direct action on the ovaries. Colloid-filled phagocytes were found at several sites in the ovaries: (1) Most of the ovarian capsule was unaffected but localized masses of phagocytes tended to collect in some regions, from which most of the connective tissue fibres disappeared, leaving only a few reticular fibres. These cells were believed to arise from resting histiocytes normally present in the tunica albuginea. (2) Scattered phagocytes containing colloid and lipid inclusions were found in the ovarian stroma. (3) Collections of phagocytes were found in three main regions in relation to the corpus luteum: (*a*) in the core where they usually contained lipid inclusions and only a little colloid; (*b*) at the periphery of the regressing corpus luteum, where they were numerous and contained both lipid and colloid; (*c*) within the meshes of the stroma, closely related to the walls of blood vessels, from which they may arise. (4) A few phagocytes were found in the stroma of the interstitial gland. The latter was often very prominent in injected animals. *R. Barer*

CIRCULATORY SYSTEM

1959. **Effect of Sympathectomy on Blood Flow in the Human Limb**
I. D. STEIN, K. HARPUDER, and J. BYER. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 499–504, March, 1948. 15 refs.

A comparison was made, by the use of plethysmographic methods of recording, of the blood flow in the foot (predominantly skin) and calf (predominantly muscle) in human patients, before and after sympathectomy of the lower limbs for peripheral vascular disease. The results show that, whereas the blood flow through skin was increased by sympathectomy, that through muscle was relatively unchanged. Exercise, local heating, and arterial occlusion and release were effective stimuli in increasing blood flow through sympathectomized muscles, suggesting that vasodilators of metabolic origin, and not the innervation, are important factors in the blood supply of muscles. The results indicate that sympathectomy is of value clinically for increasing the blood flow through skin, but not through muscle.
R. A. Gregory

1960. **Application of the Radioactive Red Cell Method for Determination of Blood Volume in Humans**
G. R. MENEELY, E. B. WELLS, and P. F. HAHN. *American Journal of Physiology* [*Amer. J. Physiol.*] **148**, 531–537, March 1, 1947. 13 refs.

Human blood volume determinations were made simultaneously by the method in which erythrocytes are labelled with radioactive iron and by the use of Evans blue dye on 28 patients. The total blood volume determined by the former technique gave a figure which is about 81% of that obtained by the dye method. The possible causes of this discrepancy are discussed.
E. F. McCarthy

1961. **Plasma Protein Fractions**
R. A. KEKWICK and N. MARTIN. *Proceedings of the Royal Society of Medicine* [*Proc. R. Soc. Med.*] **41**, 217–224, April, 1948. 1 fig., 24 refs.

The scale on which the protein constitution of biological fluids as determined by the Tiselius electrophoresis method is performed is only applicable for research processes. Usually proteins are separated by employing concentrated salt solutions (2 to 3 molar) followed by dialysis, a procedure which renders the maintenance of asepsis difficult. More recently volatile bacteriostatic solvents, methanol, ethanol, acetone, dioxane, or ether, at 0° to 10° C., with subsequent freeze drying *in vacuo* have been used. The electrophoretic pattern of human plasma is remarkably constant showing seven components: α_1 and α_2 globulins, β_1 and β_2 globulins, γ globulin,

albumin, and fibrinogen, but this constancy does not necessarily imply chemical or physiological homogeneity. With 40% ethanol at −5° C., Cohn has obtained practically pure human serum albumin. Fibrinogen-thrombin solutions, fibrin films, γ globulin, and 25% albumin solution have all been used clinically.

Although the phenomenon of the migration of particles in a medium under the influence of a constant current has been known for more than a century, it was not until 1930, when Tiselius introduced his technical refinements, that this method could be applied to the study of proteins. Ionic constitution, the concentration of the buffer solutions, and the total protein concentration affect the electrophoretic analysis. At *p*H 8·0 the protein mosaic in the normal subject has 5 main groups, the albumins, α globulins, β globulins, γ globulin, and fibrinogen. The pattern is not markedly affected by sex or age except that the foetus and newborn appear to have an excess of γ globulin. These patterns are complexes of protein with lipins and carbohydrates, nor do they correspond with salting out techniques. The changes in the electrophoretic pattern in disease are usually not a characteristic of the disease process but of the host's reaction to that process. In nephrosis α and β globulins form the major part of the circulating protein. In the early stages of simple uncomplicated infective hepatitis albumin is decreased and γ globulin relatively increased; with recovery the picture reverts to the normal although the total amount of circulating albumin may not be regained. The electrophoretic analysis of a proved case of Boeck's sarcoidosis and two cases of myelomatosis are shown; in the latter condition either one of two electrophoretic patterns may be obtained, one with predominance of β globulins, the other of γ globulins. Bilirubin may be attached to more than one protein fraction.

C. C. N. Vass

1962. **Serum Ac-globulin: Formation from Plasma Ac-globulin; Role in Blood Coagulation; Partial Purification; Properties; and Quantitative Determination**
A. G. Ware and W. H. Seegers. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 567–576, March, 1948. 3 figs., 29 refs.

A study was made of the substances in plasma and serum which accelerate the interaction of prothrombin, thromboplastin, and calcium ions. They are both globulins, that in serum being the more potent. Plasma Ac-globulin was found to be an inert protein or a proenzyme; it was changed to serum Ac-globulin by thrombin. This reaction, and the presence and properties of Ac-globulins, explains the " latent period " preceding the production of thrombin in the clotting process. After a small amount of thrombin is produced, further formation results from autocatalysis, serum Ac-globulin (more active) being formed from plasma Ac-globulin by the thrombin already formed. Large quantities of thrombin were found to destroy Ac-globulin activity. Partially purified serum Ac-globulin was obtained by addition to purified plasma Ac-globulin of a small amount of thrombin. The chemical properties of the two compounds were apparently identical. Serum Ac-globulin was very stable in bovine serum. The function of Ac-globulin in the blood-clotting mechanism is summarized by the equations:

$$\text{Prothrombin} + \text{thromboplastin} \xrightarrow{Ca^{++}} \text{thrombin}$$

$$\text{Plasma Ac-globulin} \xrightarrow{\text{thrombin}} \text{serum Ac-globulin.}$$

$$\text{Prothrombin} + \text{thromboplastin} \xrightarrow[\text{serum Ac-globulin}]{Ca^{++}} \text{thrombin.}$$

$$\text{Fibrinogen} \xrightarrow[\text{thrombin}]{} \text{fibrin.}$$

R. A. Gregory

1963. **Studies of Fluorocardiography in Normal Subjects**
F. G. Fleischner, F. J. Romano, and A. A. Luisada. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **67**, 535–539, April, 1948. 3 figs., 16 refs.

Fluorocardiography (electrokymography) is a newly developed procedure for recording on a continuous film the pulsations of various areas of the cardiovascular silhouette and the opacity changes of the lung fields on *x*-ray examination. Simultaneous phonocardiographic records are taken, which permit exact timing of the fluoroscopic pulsations. This paper is a further contribution to the study of fluorocardiography in normal subjects. Records of tracings of the ascending aorta, pulmonary veins, and pulmonary parenchyma are presented and their significance is discussed. The tracing of pulsations in the pulmonary parenchyma is comparable to a plethysmogram and is influenced by both arterial and venous changes in the blood content of the lung. From the tracings the velocity and duration of pulmonary arterial waves have been measured; the speed of the pulse in the lesser circulation has been found to be roughly one-third of the speed of pulse waves in the greater circuit. This is due to a lower pulmonary pressure and greater extensibility of the pulmonary vessels. [Those interested in fluorocardiography should become acquainted with previous work by the same authors on the subject and the appended references will be useful.]

A. I. Suchett-Kaye

1964. **Influence of Hypotension on Coronary Blood Flow, Cardiac Work and Cardiac Efficiency**
J. E. Eckenhoff, J. A. Hafkenschiel, E. L. Foltz, and R. L. Driver. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 545–553, March, 1948. 1 fig., 27 refs.

In lightly anaesthetized intact dogs, coronary blood flow was measured by the nitrous oxide method, coronary sinus blood being obtained by catheterization. Cardiac output was estimated by the direct Fick method. Hypotension was produced either by the subarachnoidal injection of procaine solution or the intravenous injection of tetraethylammonium chloride. A decrease in cardiac output and cardiac work (cardiac output × aortic pressure) occurred. Coronary blood flow decreased but the rate remained relatively high in relation to the

decreased work. Cardiac efficiency (work/oxygen consumption) was reduced but there was no evidence that the heart was less able to perform the work required of it, that is, that the hypotension was harmful to the heart.

R. A. Gregory

ENDOCRINE GLANDS

1965. **Isolation of Stilboestrol Monoglucuronide from Human Urine**

K. S. DODGSON and R. T. WILLIAMS. *Nature* [*Nature, Lond.*] **161**, 604–605, April 17, 1948. 3 refs.

Stilboestrol monoglucuronide was isolated (as the benzylamine salt) from the urine of a woman given 100 mg. of stilboestrol during 24 hours; the yield of benzylamine salt corresponded to 35% of the stilboestrol injected. Although its presence had been inferred in the urine of human beings given the drug, it had hitherto been isolated only from the urine of rabbits injected with stilboestrol. [There is some evidence that the metabolism of the synthetic oestrogens is the same in the two species and that animal results can be applied to human subjects.] *Peter C. Williams*

1966. **Effect of the Adrenal Cortex on the Sugar Metabolism.** [In English]

L. BARTA. *Annales Paediatrici* [*Ann. paediatr., Basel*] **170**, 189–199, April, 1948. 3 figs., 22 refs.

In a previous paper (*Paed. Danub.*, 1947, **2**, 88) the author reported findings with the double glucose tolerance test and the galactose tolerance test in children with endocrine disorders. In hypothyroidism or hypopituitarism the Staub effect after a second dose of glucose was missing and the galactose tolerance curve was flat.

In the present paper he performed the double glucose tolerance test before and after the administration for 5 days of 5 to 10 mg. of a synthetic adrenocortical hormone (" percorten "). The double test was chosen as more sensitive, since the short interval between the 2 series of estimations makes negligible the possibility that other factors such as absorption may vitiate the results. Any deviation from the normal in such a test may be therefore attributed to true abnormalities in the carbohydrate metabolism. Five jaundiced children were tested in this way, 1 suffering from cirrhosis confirmed by biopsy, 1 from hepatitis, 2 from septicaemia, and 1 from actinomycosis of the liver. The Takata-Ara reaction was positive in all cases, and the Weltmann reaction showed a shift to the right in all cases. In 4 out of these 5 children no Staub effect was noticed, and in 3 of these this effect appeared after the course of adrenocortical hormone.

On the basis of these results the author suggests that hepatic lesions may be accompanied by dysfunction of the adrenal cortex and that the changes in carbohydrate metabolism may be due to both. [The absence from the case notes of sufficient details of diagnosis and subsequent course, and the omission of the more sensitive liver function tests, make impossible the assessment of the nature and extent of the liver damage and of associated lesions in other systems.]

In 2 children with pituitary dwarfism and in 1 with " hypofunction of the pituitary " [though the details given are not enough to justify such a diagnosis] the same tests were performed before and after a course of adrenal cortical extract. The Staub effect, which was absent before, appeared after the administration of the hormone. Finally a case of diabetes mellitus is reported in which adrenal cortical hormone caused a marked improvement in carbohydrate metabolism. At necropsy the findings were typical of glycogen storage disease.

[Absence of important data from the reported cases make the acceptance of the author's conclusions difficult. In any case, extreme caution is required in the interpretation of therapeutic effects after administration of a biological substance in conditions the exact nature of which is not clear.] *S. Doxiadis*

NUTRITION

1967. **Effect of Vitamin D on Calcium Balance.** (L'action de la vitamine D sur le bilan calcique)

R. S. MACH, J. FABRE, and R. D. SANTA. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 453–458, May 15, 1948. 6 figs.

In order to determine the action of vitamin D on calcium metabolism, 8 subjects suffering from osteopathies were given a standard diet and the calcium balance was determined by estimating the calcium in the urine and the faeces before and after treatment with vitamin D. The vitamin was given orally in doses of 600,000 units daily, usually on several successive days, but in 2 cases at 10-day intervals over a period of several weeks. The calcium excretion was studied over periods of 8 to 19 days. In 5 cases in which the balance was negative, including 4 cases of osteomalacia, the administration of vitamin D changed the calcium balance to a positive one. In 2 cases, in which the calcium balance was positive initially, and in which atypical localized bony lesions were present, the effect of vitamin D treatment on the calcium balance was slight in 1 case and non-existent in the other. In 5 other patients without skeletal lesions or disturbances of phosphorus and calcium metabolism, the administration of vitamin D did not improve calcium retention, but on the contrary caused a calcium deficit.

Harold Jarvis

1968. **Metastatic Calcification Produced in Dogs by Hypervitaminosis D and Haliphagia**

R. M. MULLIGAN and F. L. STRICKER. *American Journal of Pathology* [*Amer. J. Path.*] **24**, 451–473, May, 1948. 17 figs., 22 refs.

At necropsy on a man who died in coma, widespread calcification of the myocardium, endocardium, gastric mucosa, lungs, kidneys, and walls of blood vessels was found (see *Abstracts of World Medicine*, 1947, **1**, 501). This man had been taking large doses of vitamin D and an alkaline salt mixture (hence the term " haliphagia ") for 6 months. In this work 16 dogs were submitted to

experiments in an attempt to reproduce the lesions noted in the patient. All dogs were kept on an adequate stock diet. Vitamin D_2 was given, usually in doses of 100,000 i.u., and alkaline salts (sal hepatica) in doses of 7·5 to 8 g. daily. Seven dogs receiving vitamin D and salt mixture and 5 dogs given only vitamin D suffered from anorexia, a loss of 32 to 61% of their original body weight, hypodipsia, apathy, and occasionally haematemesis and melaena. Two dogs on alkaline salts and two control dogs did not show these signs. In all dogs receiving vitamin D in combination, or without alkaline salts, there were varying degrees of calcification in the endocardium of the left atrium, in the walls of the aortic sinuses in the alveoli and alveolar ducts of the lungs, in the mucosa of the gastric fundus, and in the loops of Henle. In the 7 dogs receiving both vitamin D and salts there was a greater total amount of calcification in the costochondral junctions and soft tissues than in the 5 dogs on vitamin D only. Considerable atrophy of the testes, parathyroid glands, prostate gland, and lymphoid and fatty tissues was found in all dogs receiving vitamin D.

Z. A. Leitner

1969. **Production of Functional and Fatty Changes in the Liver by a Chronic Vitamin B Complex Deficiency, and Interrelationships with Protein Intake**

V. A. Drill and T. A. Loomis. *Journal of Nutrition* [*J. Nutrit.*] **35**, 333–349, March 10, 1948. 7 figs., 21 refs.

Chronic deficiency of the vitamin-B complex (0·1 g. yeast per kilo a day) in dogs fed a 20% casein diet produced changes in liver function, as evidenced by a fall in bromsulphalein excretion and a rise in serum phosphatase before the twenty-seventh week of the study. Animals given the same amount of yeast but a 41% casein diet showed no such change, even when the experiment was prolonged to 50 weeks. In controls receiving the same number of calories as the yeast-deficient animals but adequate B complex no change in hepatic function and no abnormal histological appearances in the liver were observed. The livers of the dogs showing evidence of impairment of function contained large fat globules, generally distributed throughout the lobule, but no necrosis. Treatment with yeast restored liver function to normal and led to disappearance of the fat globules in the liver, even though protein and calorie intakes were restricted.

O. L. V. de Wesselow

1970. **Action of Vitamins on Metabolism. II. Action of Vitamin D.** (Influenze vitaminiche sul ricambio energetico. II. Azione della vitamina D)

R. Pachioli. *Clinica Pediatrica* [*Clin. pediat., Bologna*] **30**, 145–152, March, 1948. 21 refs.

The author reviews the literature on the subject of hypothyroidism in rickets (both in the human subject and in the experimental animal) and on the action of vitamin D in increasing the basal metabolic rate (B.M.R.) of the rachitic patient. He has studied the behaviour of the B.M.R. of 14 healthy children (aged 6 to 13 years) after injection of 0·015 g. (600,000 i.u.) of vitamin D_2 (calciferol). The subjects of the experiment were divided into 2 groups of 4 and 10 children respectively. The children of 1 group were given only 1 injection, while the second group received a second injection of vitamin D after a week. The B.M.R. was determined by means of a Benedict-type closed circuit apparatus, while the body surface was calculated from the DuBois formula. In each case 1 control determination was carried out, followed by 3 determinations at weekly intervals, starting 1 week after the injection of vitamin D. The first determination after injection of vitamin D showed a moderate increase of the B.M.R. (average approximately +5%) in 12 of the 14 patients. The second determination revealed a fall almost to control values in all the subjects who received only 1 injection, while in the children given a second injection the rate of fall was slower. No new rise followed the second injection. From the results of his experiments which are in accord with experimental evidence offered by other workers, the author concludes that the thyroid may possibly be temporarily stimulated by vitamin D.

P. E. Polani

1971. **The Effect of Isocaloric Substitution of Alcohol for Dietary Carbohydrate upon the Excretion of B Vitamins in Man**

R. E. Butler and H. P. Sarett. *Journal of Nutrition* [*J. Nutrit.*] **35**, 539–548, May 10, 1948. 21 refs.

In confirmation of previous studies by other workers on rats and pigeons, the present authors have found that replacing corn starch and sugar isocalorically by alcohol in an adequate diet increased the urinary excretions of thiamin, N′-methylnicotinamide, and nicotinic acid. The urinary excretions of nitrogen, tryptophan, creatinine, pantothenic acid, and pteroylglutamic acid were not affected. The carbohydrate diet greatly increased the urinary excretion of 4-pyridoxic acid, probably because pyridoxine was synthesized in the gut. The authors point out that this sparing action of alcohol (which provided 800 Calories daily) on thiamin and nicotinic acid may not occur when excessive amounts of alcohol are consumed with a diet providing inadequate calories.

H. M. Sinclair

1972. **The Relation of Diet Composition and Vitamin C to Vitamin A Deficiency**

J. Mayer and W. A. Krehl. *Journal of Nutrition* [*J. Nutrit.*] **35**, 523–537, May 10, 1948. 1 fig., 21 refs.

The authors have previously shown that in young rats the effect of a diet deficient in vitamin A is to decrease the efficiency of utilization of food; there are also symptoms which respond to administration of ascorbic acid, although the rat synthesizes this vitamin. They have now investigated the effect of replacing dietary sucrose by iscaloric amounts of protein, of saturated fat, or of unsaturated fat. Increasing the protein decreases survival time and the efficiency of utilization of food but increases the scorbutic signs. It is suggested this is due to an increased need for ascorbic acid. The authors also show that in animals on a diet deficient in vitamin A the amount of ascorbic acid in blood and liver is less than half that in normal rats.

[This interrelation of vitamin A and ascorbic acid is interesting and may help to explain some anomalous results of vitamin-A deficiency in man. As the authors point out, it has a very important bearing on the methods of bioassay of vitamin A in which rats are used.]

H. M. Sinclair

1973. **Effects of Young Men Consuming Restricted Quantities of B-complex Vitamins and Protein, and Changes Associated with Supplementation**

G. H. Berryman, C. R. Henderson, N. C. Wheeler, R. C. Cogswell, J. R. Spinella, W. E. Grundy, H. C. Johnson, M. E. Wood, C. W. Denko, T. E. Friedmann, S. C. Harris, A. C. Ivy, and J. B. Youmans. *American Journal of Physiology* [*Amer. J. Physiol.*] **148**, 618–647, March 1, 1947. 10 figs., 39 refs.

Seven normal males, 23 to 28 years old, after an initial period of normal dieting lasting for 3 months, were put on an experimental diet for 35 weeks. The total calorific value of the daily experimental diet was approximately 3,000 Calories, and the diet contained 45 g. of protein, mainly vegetable, 0·5 mg. of aneurin, 0·3 mg. of riboflavin, 5·8 mg. of nicotinic acid, and unusually small amounts of the lesser known B-complex vitamins—folic acid, pyridoxine, pantothenic acid, and biotin. After 5 weeks of the experimental diet 2 of the subjects were treated as controls and had their diet supplemented with animal protein and crystalline vitamin preparations to restore it to the pre-experimental nutritive level. Placebos were given simultaneously to the other subjects. The diet of 3 of the latter was supplemented with aneurin after 15 weeks, and that of the remaining 2 subjects was similarly supplemented after 18 weeks of the experimental period. Protein, riboflavin, nicotinic acid, folic acid, pyridoxine, pantothenic acid, and biotin were then added either together or in a stepwise manner. After 20 weeks' supplementation the subjects were placed on a rich diet for 3 weeks.

The control subjects either showed no change from the condition observed during the initial period of adequate dieting or else a moderate improvement. After 15 weeks of restricted diet, the experimental subjects had a decreased capacity for physical work and elevated pulse rates at rest and after exercise contrasted with their condition in the initial period. Definite evidence of specific deficiencies was not observed, but suggestive signs and symptoms were present. These included mouth ulcers, scrotal dermatitis, and motor disturbances of the small intestine, cramps of the extremities, lassitude, insomnia, and sore mouth. Body weight was moderately decreased and nitrogen equilibrium was maintained. Tendencies to hysteria, depression, and hypochondriasis were manifested. The urinary vitamin-B-complex excretion was low. During the period of supplementation there was a gradual return to normal. The improvement was too gradual to permit of the definite association of any nutrient with the disappearance of any pathological sign or symptom.

" Sulphathalidine ", 4 g. per day, was given from the thirty-third to the thirty-fifth week of the experimental period; this resulted in a decrease in the coliform organisms of the faeces accompanied by a decrease in faecal *Lactobacillus casei* factor and biotin. The aneurin content of faeces was also decreased in 3 subjects and 2 of these excreted less riboflavin and pantothenic acid than before the administration of sulphathalidine. Urinary levels of these substances were not significantly affected. *E. F. McCarthy*

1974. **Effect of Administering Agenized Amino Acids and Wheat Gluten to Dogs**

G. E. Newell, S. N. Gershoff, F. H. Fung, and C. A. Elvehjem. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 637–644, March, 1948. 18 refs.

No consistent or significant differences were observed between values for hemoglobin, hematocrit, red blood cell count, white blood cell count, prothrombin time, glucose, calcium, phosphorus, sulfur or vitamin C of the blood of dogs when fed agenized wheat gluten and when fed the basal ration. A definite increase in the blood magnesium and potassium was observed when the agenized wheat gluten was fed. Selenium toxicity in dogs is not related to the condition of running fits. Injection of magnesium, potassium or calcium pantothenate had no effect in preventing or lessening the intensity of the seizures. Various agenized amino-acids were fed as part of a ration, by stomach tube or intravenously, but none of the 28 animals tested developed fits as a result of this treatment.—[Authors' summary.]

1975. **A Growth-retarding Factor in Maize Bran**

A. Borrow, L. Fowden, M. M. Stedman, J. C. Waterlow, and R. A. Webb. *Lancet* [*Lancet*] **1**, 752–753, May 15, 1948. 1 fig., 8 refs.

Workers in the United States have shown: (1) that the association of pellagra with consumption of maize cannot be explained by simple deficiency of nicotinic acid; (2) that addition of maize to the diet of rats retards growth; and (3) that maize contains a toxic substance. The present authors find that the bran of maize, but probably not the flour, contains a toxic substance that retards growth in mice. The retardation is prevented if nicotinic acid is added to the diet. *H. M. Sinclair*

1976. **Experimental Studies on the Intravenous Injection of a Fat Emulsion into Dogs**

H. C. Meng and S. Freeman. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 689–707, June, 1948. 3 figs., 45 refs.

Much work has already been done on the effect of intravenous injection of emulsions of fat. In all cases, toxic manifestations and complications such as emboli or liver damage have been observed. This paper describes the preparation of a stable, finely divided emulsion and a study of its physiological effects and utilization in dogs. After preliminary tests, butter oil was selected as the fat to be used. It was emulsified with a mixture of a proprietary surface agent (" span 20 "), a proprietary preparation of soya phosphatides (" asolectin "), and sodium cholate. The resulting stable and fine emulsion contained 10% butter oil, 0·5% span 20, 0·4% asolectin,

and 0·1% sodium cholate. Neither the emulsifying agents alone nor the fat emulsion caused any fall in blood pressure in dogs, but both increased the secretion of urine and bile. Both also increased the flow of thoracic duct lymph, but only the fat emulsion increased the total output of lipids. Daily intravenous infusion of the emulsifying agents for 4 weeks had no toxic effect. Daily intravenous infusion of the butter fat emulsion to dogs on a fat-free diet led to a gain in weight and a positive nitrogen balance as in the control period. The serum lipids were not increased after the injection of the emulsifying agents but did increase for up to 17 hours after the injection of the emulsion. The increase in total fatty acids was high whilst that of the cholesterol and phospholipids was slight. Histological examination of animals injected with the emulsifying agents revealed normal liver and kidneys. Two animals receiving the fat emulsion had normal lungs and kidneys, but one had fat granules in the liver cells. *J. Yudkin*

1977. **The Metabolism of Glucose in Starvation and Water Deprivation**
A. Wollenberger and M. A. Linton. *American Journal of Physiology* [*Amer. J. Physiol.*] **148**, 597–609, March 1, 1947. 2 figs., 33 refs.

After a period of starvation or severe restriction of carbohydrate intake, glucose tolerance is diminished. The response to glucose administration after a period of fasting is characterized by a diabetic blood sugar curve and a delayed rise in the respiratory quotient. The authors have investigated intermediary carbohydrate metabolism under these conditions. In one series of experiments studies were made on the oxidation of administered glucose after 6 to 8 days' starvation during which a litre of water was consumed daily. The blood sugar curve was of the diabetic type, and the fall in plasma inorganic phosphate which follows glucose injection was abnormally slow and prolonged beyond the usual limits. The amounts of pyruvic and lactic acids which normally increase after glucose ingestion showed no change, or decreased slightly, in the initial stages when glucose accumulation was very rapid. After a delay of 1 hour, pyruvic and lactic acid levels rose slowly, reaching a maximum in 3 hours. The normal retention of urinary inorganic phosphate which follows glucose administration was postponed or absent for a 4-hour period. A retarded rise in respiratory quotient to an unusually low level occurred. These findings are interpreted as signifying a failure in the formation of pyruvate and lactate from ingested glucose.

Other subjects received 606 to 685 Calories of sugar and fat mixtures and 400 ml. of water daily, supplemented in some cases with aneurin (thiamin) hydrochloride and sodium chloride. After glucose administration the initial rise and subsequent fall in the blood sugar curve were exaggerated, causing severe hypoglycaemia. Blood pyruvate and lactate showed at the same time a prolonged and exaggerated rise which suggested formation from ingested glucose. The daily intake of small amounts of glucose is regarded as probably essential for the hypoglycaemic response.

The abnormal accumulation of pyruvate and lactate after partial starvation and water deprivation may be due to inadequate removal as a result of aneurin deficiency. The addition of aneurin hydrochloride, 5 mg. daily, had no influence on the response to glucose in these cases.
E. F. McCarthy

1978. **Role of the Kidney in Fat Metabolism.** (La intervención del riñon en el metabolismo de la grasa)
C. Jimenez Diaz and H. Castro Mendoza. *Revista Clínica Española* [*Rev. clín. esp.*] **29**, 84–89, April 30, 1948. 2 figs., 8 refs.

In 4 dogs after double nephrectomy under ether anaesthesia a hyperlipaemia developed affecting all lipid fractions and running parallel with the development of uraemia. The hyperlipaemia was prevented in 3 dogs when 5 ml. of a glycerin extract of pigs' kidneys (representing 1·37 g. of kidney tissue) was injected. The authors claim that this demonstrates the presence of a substance in kidney tissue which controls lipaemia. [Such a conclusion seems to be unjustified on the evidence presented.] *A. C. Frazer*

1979. **Studies of the Function of the Liver in Carbohydrate Metabolism.** (Studien über die den Kohlehydratstoffwechsel regulierende Tätigkeit der Leber)
A. Iizuka. *Tohoku Journal of Experimental Medicine* [*Tohoku J. exp. Med.*] **49**, 131–166, Oct. 17, 1947. 12 figs., bibliography.

In order to study the function of the liver in intermediary metabolism of carbohydrates, samples of blood entering and leaving a rabbit's liver were injected intravenously into another rabbit and the values of blood sugar and blood lactic acid determined. Instead of entering blood, however, carotid blood was used [a substitution open to criticism]. The carotid blood of normal rabbits caused hyperglycaemia and hypolactacidaemia; the blood from the liver veins caused hypoglycaemia and greater hypolactacidaemia. If liver function was previously damaged by ligation of the bile duct, by phosphorus poisoning, or by blocking the reticulo-endothelial system with India ink, the injection of either carotid blood or blood from hepatic veins caused hyperglycaemia and hyperlactacidaemia. Hence the liver checks the hyperglycaemic effect of the blood and diminishes the content of lactic acid. Carotid blood of rabbits which had received large doses of insulin (5 units per kilo body weight) caused pronounced hypoglycaemia and hypolactacidaemia; blood from hepatic veins acted in the same way but in lesser degree; thus, passage through the liver weakens the effects of insulin. When the liver was damaged by the procedures mentioned above this effect disappeared. Carotid blood from rabbits given adrenaline (0·5 mg. per kilo body weight) increased the blood sugar slightly and diminished the lactic acid; blood from hepatic veins greatly diminished both; thus, the effect of adrenaline is checked by passage through the liver.
O. Neubauer

NERVOUS SYSTEM

1980. **Pain Sensibility in Deep Somatic Structures**
W. H. FEINDEL, G. WEDDELL, and D. C. SINCLAIR. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **11**, 113–116, May, 1948. 7 figs., 16 refs.

This work was undertaken to find out whether there was an anatomical basis for Lewis's suggestion that two separate systems of nerves conveyed pain sensation from the skin and from deep structures, such as muscles and periosteum. The innervation of normal skin is by a close network of nerve endings with overlapping terminals derived from different axons supplying any one area of skin. In skin from which abnormal pain sensation is elicited the adjacent terminal fibres do not interweave, the nerve terminals being isolated from one another. The innervation of the deep structures was investigated by the authors' technique of deep perfusion with methylene blue (*Brain*, 1947, **70**, 495). In muscle, fine beaded fibres run either in fibrous tissue septa or as " accessory " fibres to muscle spindles. These form a very loose meshwork and the individual neural terminals are invariably isolated from one another. There is a similar type of nerve arrangement in fascia and in periosteum but the meshwork is denser than in muscle and some adjacent terminals interweave. The authors consider that the different types of pain produced from the skin and from the stimulation of deep somatic structures can be satisfactorily explained by the difference in the arrangement of the nerve terminals in these structures, and that Lewis's postulate of two separate pain-conducting systems of nerves is not necessary.

J. W. Aldren Turner

1981. **Observations on Cutaneous Hyperalgesia, with Notes on Related Reactions**
J. A. HARPMAN. *Brain* [*Brain*] **71**, 34–47, March, 1948. Bibliography.

The author confirmed that cutaneous hyperalgesia surrounding epidermal injuries is dependent upon a peripheral neural mechanism involving the nerve fibres and nerve endings subserving pain. There is a peripheral interneuronal spread of the phenomenon underlying skin hyperalgesia and flare. Relations of skin hyperalgesia to superficial veins, vasodilatation, vasoconstriction, and circulatory arrest are described and the phenomena correlated with observations on the spread through tissue spaces and lymphatics of adrenaline injected intradermally and the effects of circulatory arrest on this spread. Factors relating the circulatory system to cutaneous hyperalgesia include temperature, distension through vascular engorgement, and blood and lymph flow. It is concluded that the production or liberation and the spread of a substance are also concerned in the mechanism of hyperalgesia. The beneficial effects of vasodilatation on some pain syndromes may be due to the action of increased blood flow on this substance. Implications of these findings are discussed, together with the related reactions—flare, itching, and hypoaesthesia. [This is a difficult paper to abstract satisfactorily. It is largely a critical review of the subject amplified by the author's experimental work on the hyperalgesia following intradermal injuries.]

N. S. Alcock

1982. **The Influence of Alterations in Posture of the Limbs on Cortically Induced Movements**
E. GELLHORN. *Brain* [*Brain*] **71**, 26–33, March, 1948. 5 figs., 6 refs.

The author determined the effect of the posture of a limb on cortically induced movements in monkeys anaesthetized with " dial "- urethane. A Goodwin stimulator was used to stimulate the cortex by means of bipolar silver electrodes 2 mm. apart, either a threshold stimulus or one slightly above being used. The stimulus was applied for 5 seconds to various cortical foci by means of the Horsley Clarke apparatus. Before the stimulus a joint of the fore-limb or hind-limb was placed either at an acute or obtuse angle. The cortically induced movement was observed and the activity recorded by electromyograms.

The hamstrings responded slightly more and earlier when the knee was bent at 110 degrees than when it was at 45 degrees. The quadriceps showed the converse result. An increase in the initial length of a muscle thus enhances its responsiveness to a standardized cortical stimulus. This holds good also for the elbow, ankle, and hand muscles. It is suggested that these changes are due to proprioceptive impulses. The number of discharging afferent nerve fibres as well as their frequency increases with increasing length of the muscle and gives rise to interaction (facilitation) with the cortically induced impulses. Whether this interaction takes place only at the spinal level or also at the cortical level remains to be determined.

N. S. Alcock

1983. **Influence of Repeated Anoxia, Electroshock and Insulin Hypoglycemia on Reactivity of Sympathetico-adrenal System**
E. GELLHORN and H. SAFFORD. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 74–79, May, 1948. 2 figs., 19 refs.

Rats were subjected to a standard anoxia test involving 5 consecutive periods of 25 minutes each at 280 mm. Hg barometric pressure. Their blood sugar values were determined. The rise in blood sugar due to anoxia increased as a result of repeated series of exposures to low barometric pressure; this effect disappeared after a rest period of 2 weeks. Electrical convulsions greatly increased the hyperglycaemic response to the standard anoxia test. Repeated induction of insulin coma brought about a diminished or absent response to the anoxia test; in these rats, adrenaline failed to produce a hyperglycaemic response. The results are interpreted as signs of altered balances between the sympathetico-adrenal and vago-insulin control systems of the organism.

A. Schweitzer

Pharmacology and Therapeutics

1984. **Variations in Dermal Absorption with Age**
J. STRAUSS and H. NECHELES. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 612–617, May, 1948. 27 refs.

In the Michael Reese Hospital, Chicago, the dye "Evans blue" was injected intradermally into 137 healthy subjects, approximately equal as to the sexes and of all ages up to 90 years. The injections were given into the middle third of the anterior aspect of the forearm with a short No. 25 hypodermic needle on a tuberculin syringe in doses of 0·1 ml. of sterile solution of Evans blue in normal saline. The optimum strength of the solution was arrived at by trial and error and is not specified. An injection was considered to be truly intracutaneous if a blanched wheal appeared having a surface like orange-peel. A circumscribed stained area resulted which disappeared in a variable time (maximum 48 hours). Measurements were taken as follows: The stain was outlined in ink and a strip of clear celluloid was pressed upon it. The area of the mark thus made was measured with a planimeter. This procedure was carried out immediately after the injection and repeated 4, 24, and 48 hours later. Thus four readings were obtainable on the same strip from the same subject. From the coordinated results it appears that the initial wheal is smaller in young persons, while in older subjects the wheal is larger and the dye disappears more rapidly. Attempts are made to explain these phenomena on mechanical grounds, although it is admitted that chemical and biological factors must exist which are little understood at present. [There is a valuable review of the literature and an extensive bibliography on many related subjects.] *T. E. Graham*

1985. **Preponderance of Anti-adrenaline Effect over Anti-acetylcholine Effect in Local Analgesics.** (De la prépondérance de l'action anti-adrénalinique sur l'effet anti-acétylcholinique des anesthésiques locaux)
E. FROMMEL, M. FAVRE, and F. VALLETTE. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **76**, 341–350, May 1, 1948. 2 figs., 21 refs.

Clinical use of intravenous procaine in various pathological conditions prompted this study. Intracardiac injections of local analgesics have been made in guinea-pigs, and estimates made of their relative powers of preventing the electrocardiographic changes seen after injection of adrenaline or acetylcholine. Minimal intracardiac doses of adrenaline and acetylcholine causing such changes were, respectively, 5 μg. per kg. and 200 μg. per kg. Procaine (12 mg. per kg.) and "nupercaine" (0·5 mg. per kg.) neutralized the effect of about 5 such minimal doses of adrenaline but only of 2½ minimal doses of acetylcholine. Cocaine (4 mg. per kg.) did not reduce the adrenaline effect but abolished the action of 2 minimal doses of acetylcholine. Procaine also prolongs the refractory period of frog heart muscle. The results are considered in relation to clinical use of procaine in "sympathotonic" and "vagotonic" conditions. *Derek R. Wood*

1986. **The Metabolism of *p*-Aminosalicylic Acid in the Organism of the Rabbit**
A. VENKATARAMAN, P. R. VENKATARAMAN, and H. B. LEWIS. *Journal of Biological Chemistry* [*J. biol. Chem.*] **173**, 641–651, April, 1948. 27 refs.

p-Aminosalicylic acid (PAS) was administered by stomach tube to rabbits either as the sodium salt in solution or as free acid in fine suspensions, or was injected intramuscularly as the sodium salt in solution. Chemical purification of the substance used, and methods for its colorimetric analysis, are described. No toxic symptoms appeared on administration of 150 mg. of PAS per kilo body weight to male rats daily for 2 weeks. In rabbits negligible amounts appeared in the faeces, indicating complete absorption. After oral ingestion of the compound 53 to 80% could be accounted for in the urine. After intramuscular injection, 90% was recovered from the urine. Of the total amount excreted 70 to 90% was recovered in the first 6 hours, during which 55 to 80% was in the acetylated form. Only 40% was acetylated when the compound was administered parenterally, probably because of rapid excretion. PAS did not undergo decarboxylation *in vitro* on incubation with stomach and intestinal contents from rabbits or rats, though a small amount was acetylated. No indication of conjugation of PAS with ethereal sulphate, glucuronic acid, or glycine was found, though small discrepancies in the analyses indicated that small amounts of an unknown metabolite were present. It was concluded that the chief mechanism of detoxication was acetylation. *P. B. Marshall*

1987. **Evaluation of a New Sedative Drug (3,3-Diethyl-2,4-Dioxopiperidine)**
A. E. PARSONNET, A. BERNSTEIN, E. KLOSK, E. HIRSCHBERG, S. H. RUBIN, and L. A. PIRK. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 602–611, May, 1948. 2 figs., 7 refs.

The new drug, "sedulon" (3,3-diethyl-2,4-dioxopiperidine), was given to 5 men and 7 women, of ages from 27 to 64, suffering from hypertension. One obtained relief with 0·375 g. a day, but the others required 0·75 g. The sedative effect came on after one-half to 1 hour, and lasted for 3 to 4 hours. The drug was less soporific than phenobarbitone, given in doses to produce equal sedative effects. There was no action on the raised blood pressure in these cases. Of these 12 patients, 8 have been treated

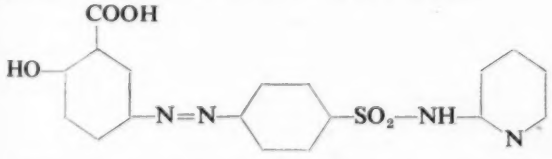
for from 6 to 12 months at the same dose level and no signs of tolerance or of addiction have been found. The blood picture has been examined frequently; no changes attributable to the drug have occurred, and no other toxic phenomena have been observed. Another 50 patients, suffering from nervous or mental instability, have been under treatment for from 3 to 5 months. Again, one has only required 0·375 g. a day, but the remainder have required 0·75 g. to produce good, but not excessive, sedation. In one case, nausea and dizziness occurred but ceased on withdrawal of the drug. It did not reappear on further administration. Apart from this, no toxic effects were seen.

In dogs, it has been shown that sedulon is excreted in the urine in an oxidized form, 3,3-diethyl-2,4-dioxotetrahydropyridine (" N.U. 903 ") to the extent of about 7 to 8%. The urinary excretion in normal men has been examined. A fluorometric method was applied to 24-hour specimens of urine to determine the amounts of N.U. 903 excreted after administration of that substance and of sedulon. About 9% of the dose of N.U. 903 given and an amount of N.U. 903 corresponding to about 6·7% of the dose of sedulon were thus excreted. It is suggested that the action of sedulon is due to its conversion to the oxidized form in the body.

Reginald St. A. Heathcote

1988. **Therapeutic Effect of Azo Compounds of Salicylic Acid with Sulphonamides.** (Ueber die therapeutische Wirkung der Azoverbindungen der Salicylsäure mit Sulfapräparaten)
N. SVARTZ. *Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften* [*Bull. schweiz. Akad. med. Wiss.*] **3**, 311–319, April, 1948. 7 figs.

Azo compounds of salicylic acid with sulphonamides have been prepared. For example, with sulphapyridine the azo compound has the following structure:



This compound has been called " salazopyrin ", and contains about 60% of sulphapyridine and 40% of salicylic acid. Similar azo compounds with sulphathiazole and sulphapyrimidine were prepared. The acid, but not the alkaline, azo compounds were shown, by means of fluorescent microscopical examination of the tissues (aorta and skin) in mice, to have a marked affinity for connective tissue. Since both ulcerative colitis and rheumatic polyarthritis are diseases characterized by changes in the connective tissue, salazopyrin had been employed in the treatment of these conditions over a period of years (1940–5) in some hundreds of cases. The total daily dose was usually about 6 g. (6 doses of 1 g.). No renal complications have been observed. Out of 124 patients with ulcerative colitis 108 have shown improvement. Similarly, out of 100 with acute polyarthritis 92 have been rendered symptom-free.

[It is of interest to note that in the discussion at the end of the paper Holsti of Helsinki states that he was not able to confirm these very favourable results. He had to discontinue treatment in his cases of chronic arthritis and ulcerative colitis because of toxic symptoms with consequent relapses.] *R. Wien*

1989. **The Response of Isolated Hypodynamic Myocardium to Inotropic Drugs**
L. J. SCIARINI, E. M. ACKERMAN, and W. T. SALTER. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **92**, 432–442, April, 1948. 5 figs., 12 refs.

A number of cardiac glycosides were compared as regards their efficiency in increasing the contractions of the fatigued papillary muscle of the right ventricle in the cat. In each experiment the concentration of the glycoside was increased every hour, the increase in log concentration being equal at each addition, until a toxic level was reached. The various glycosides were each compared in this way with a standard sample of ouabain. From the results the following equation is calculated, in which G is the concentration of the glycoside, M is its negative log potency, " a " is a constant given by the response of the individual muscle to ouabain, and R is the ratio of the contraction to the maximal contraction obtainable:

$$\log G + \log M + \log a = 0{\cdot}5 \log \frac{R}{1-R}.$$

V. J. Woolley

1990. **Quantitative Demonstration of Absorption of Calcium from the Rectum by Measurement of Tone in the Gravid Human Uterus.** (Quantitativer Nachweis rektaler Calcium-Resorption durch Tonusmessung am graviden menschlichen Uterus)
H. SAUTER. *Schweizerische Medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **78**, 404–407, May 1, 1948. 6 figs., 28 refs.

It is pointed out that determination of serum calcium is inadequate for determining the amount of calcium absorbed. Investigations of others in which the radioactive isotope Ca^{45} was used showed that 30 to 90% of calcium given orally may be absorbed. In order to determine by a simple method whether and to what extent calcium is absorbed if given by the rectal route, its effect in increasing the tone of the pregnant uterus was utilized. By means of Frey's hysterotonograph (Sauter, *Gynaecologia*, 1946, **121**, 247) the tone of the uterus was quantitatively investigated in women during the last few weeks of pregnancy. Calcium was administered as " purvit-calcium " suppositories, containing calcium gluconate and calcium laevulinate 1 g., sodium phosphate 0·003 g., vitamin A 4,000 i.u., vitamin D 2,000 i.u.; the effect of such suppositories was compared with that of intravenous injections of various amounts of a 10% solution of calcium gluconate. The smallest effective dose of intravenously injected calcium gluconate was between 0·7 and 0·8 g., irrespective of whether this was given in one single dose or in divided doses within

20 minutes. Suppositories containing 0·8 g. calcium gluconate were effective, whereas those containing 0·65 g. had no effect. It is emphasized that the threshold value of 0·8 g. was found so constantly that the finding suggested an " all-or-nothing " law. It is concluded that at least 80% of the calcium contained in the suppositories was absorbed. The vitamins contained in the suppositories had no effect; whether they increased the absorption of calcium could not be decided. *A. Schott*

1991. **Studies on the Activation of Oxytocics.** (Estudios sobre la activación de los occitócicos)
J. Botella Llusiá and A. Maldonado del Castillo. *Revista Clínica Española* [*Rev. clín. esp.*] **27**, 426–432, Dec. 31, 1947. 9 figs., 29 refs.

The authors have carried out an experimental and clinical study based on the work of Velázquez and others, who found that procaine in concentrations of 1 in 20,000 to 1 in 15,000 increases considerably the oxytocic response of isolated uterine muscle to posterior pituitary hormone, and who believe that the *p*-aminobenzoic acid part of the procaine molecule has a weakly oxytocic effect, and that the diethylaminoethanol fraction sensitizes the uterus to pituitary extract.

The experimental work was carried out with strips of uterine tissue removed from the non-gravid uterus obtained at operation, and from the gravid uterus at the time of lower-segment Caesarean section. In order that the tissue might be fresh the work was done near the operating theatre, and the strips were placed in oxygenated Tyrode solution at 37° C. At the end of 2 hours there was spontaneous contractility and a good response to the drugs which lasted for a further 1 hour to 1½ hours. The authors consider that the technique employed by others of keeping the tissue at 4° C. until used is unfavourable to muscle function, and they have not used Locke's solution. Forty-five experiments were carried out with 28 strips of isolated uterus. These showed that doses of 0·01 ml. of 1 in 100 procaine in a bath containing 250 ml. had no action on either the gravid or the non-gravid uterus. This result differs from that obtained in rodents, in which procaine has a weak oxytocic action, and this difference can be explained by the different distribution of the cholinergic and adrenergic innervation in the human and the rodent uterus. Injections of 0·01 of a Voegtlin unit of posterior pituitary extract produced at the most only a slight oxytocic reaction in the gravid and non-gravid uterus, but the same amount used after procaine resulted in a strong oxytocic response with increase of tone and spontaneous contractions. These findings prove that in the human uterus procaine sensitizes the muscle to the oxytocic action of posterior pituitary extract, although it lacks the direct oxytocic reaction found by Velázquez in rodents.

The clinical experiments were carried out in 68 patients, mainly in multigravidae with inertia towards the end of the first stage or in the second stage. External tocography was carried out with a modified Frey apparatus, the tracings being recorded on paper with the amount of uterine tone indicated by concentric circles. Procaine was given by the subcutaneous, epidural, and intravenous routes, and by itself was found to have no oxytocic action. When given intravenously in doses of 0·05 g. together with, or followed by, 1 unit or 2 units of pituitary extract, however, it produced a strong uterine response. In cases in which the pituitary extract was given first, the oxytocic effect was only found after the procaine had been given. The authors conclude that both the *in vitro* and *in vivo* experiments show that procaine sensitizes the uterus but does not act as an oxytocic. They consider these findings of great importance, for an oxytocic effect can be obtained with only a small dose of posterior pituitary extract. Finally they suggest that procaine acts by inhibiting cholinesterase. *Bryan Williams*

1992. **Studies of the Diuretic Action of Formoguanamine and its Toxicity.** (Étude de l'action diurétique de la formoguanamine et de sa toxicité)
R. S. Mach and J. P. Dubois. *Praxis* [*Praxis*] **37**, 317–323, May 6, 1948. 6 figs., 5 refs.

" Formoguanamine " (2,4-diaminotriazine) is known to possess marked diuretic properties. In rats and bitches this exceeded the diuretic action of urea many hundred times, almost equalling that of " salyrgan ". Doses of 15 mg. per kilo body weight 6 times a week for 12 weeks were well tolerated by bitches, without loss of weight and without disturbance of the body temperature regulation or alteration of the blood picture. No change in kidney and liver function was observed, and necropsy revealed nothing abnormal. In 4 people who took 8·5 to 10 mg. formoguanamine per kg. increase of urine secretion began 1 hour later and continued at a high level for 3 hours in 2 of the volunteers. The 2 others complained of lumbar pain and unusual thirst. The urine contained crystals of " ammelide ", a breakdown product of formoguanamine, and a rather large amount of chlorides.

This paper reports observations made on 56 patients suffering from water retention due to cardiac, renal, or hepatic disease. In the earlier stages of the investigations doses of 15 to 30 mg. per kg. were administered, later the maximal dose was reduced to 10 mg. per kg. The blood urea was normal in every case, and there were no erythrocytes in the urine. The drug was given only once to the vast majority of patients. The data collected included urine output for 2 days before, and 4 days after, the administration of the drug and chloride and urea excretion in three 48-hour periods during the same period. A marked increase of water elimination was recorded in 36 out of 56 patients in the first 48-hour period after taking the drug (with no change in 6, and an adverse balance in 14); at the end of 96 hours the increase had been maintained in 34 patients (with no change in 4 and a decrease in 18 patients). The chloride excretion was estimated in 49 patients: after 48 hours it showed an increase in 32, no change in 1, and a decrease in 16, whereas after 96 hours the increase was still maintained in 26 patients with a decrease in 23. The corresponding figures for urea excretion are: after 48 hours an increase in 17, no change in 3, a decrease in 29; after 96 hours an increase in 13, decrease in 31 (5 specimens were lost). In 7 patients a simultaneous rise of urine volume and

chloride and urea excretion was seen. There was no parallelism between the dosage and the results obtained; the addition of ammonium chloride did not enhance the diuretic action of the drug. In 12 patients toxic effects were observed: the dose had been within the optimal limit or only slightly above. Three times the decrease in urine output was followed by no serious side-effect. In 9 patients the decrease went on to complete anuria or oliguria of such a degree as to give rise to azotaemia with grave clinical signs. It seems as if untoward signs appeared in those patients who had been given a second dose of the drug after a good response to the first one. The drug which had been marketed by the manufacturers is now available for experimental purposes only.

L. H. Worth

1993. **The Pharmacology of Compounds Structurally Related to Hydroxytyramine**

A. M. LANDS, V. L. NASH, B. L. DERTINGER, H. R. GRANGER, and H. M. MCCARTHY. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **92**, 369–380, April, 1948. 5 figs., 15 refs.

The pharmacological properties of 12 substances related to adrenaline have been examined and compared with those of adrenaline. Effects were determined on blood pressure in dogs, on the heart in dogs and the isolated heart of the frog, on the bronchi in a perfused guinea-pig lung, on the isolated ileum of the guinea-pig, and on the isolated uterus of rabbit and guinea-pig. Acute (72-hour) toxicity was determined by intraperitoneal injection in mice. The results are tabulated. *dl*-Noradrenaline is a more potent vasopressor than *dl*-adrenaline but is less potent than *l*-adrenaline. Bronchodilatation and all inhibitory effects are associated with the presence of a hydroxyl group attached to the β-carbon atom; this activity is increased by presence of an N-alkyl group. Adrenaline caused excitation of the guinea-pig uterus [it is not stated whether the guinea-pig was virgin or not].

V. J. Woolley

CHEMOTHERAPY

1994. **New Antibacterial Diamidines**

R. WIEN, J. HARRISON, and W. A. FREEMAN. *Lancet* [*Lancet*] **1**, 711–712, May 8, 1948.

Preliminary observations on two new compounds, 2,2′-dibromopropamidine and 2-iodohexamidine, compared with propamidine and hexamidine, are reported with reference to their possible use in surface infections. Tests of bacteriostatic activity by turbidimetric serial dilution and Fleming's slide-cell methods, bactericidal activity by subcultivations on to trypsin-digest agar from tubes of the bacteriostatic tests, and fungistatic activity, by incorporation of serial dilutions in 2% glucose-agar and inoculation with fungus spores, showed that the halogenated derivatives were more active than the parent compounds against bacteria but not against fungi. The high activity against Gram-positive bacteria was not reversed by blood or serum. The maximal bactericidal activity was attained in 6 to 10 hours and the LT 50 (time required to reduce the count by 50%), with *Staphylococcus aureus*, was about 70 minutes. Increasing alkalinity (*p*H 6·4 to 7·6) favoured bacteriostasis. Serial subcultures with one diamidine *in vitro* enabled the organisms to develop resistance to all, but these organisms were still penicillin-susceptible (*Streptococcus pyogenes* and *Staph. aureus*), and penicillin-resistant organisms were susceptible to the diamidines. The halogenated compounds are more toxic intravenously and less subcutaneously than the parent compounds. A comparison of the four diamidines with 5-aminoacridine as regards toxicity to human phagocytes and chick embryos and the concentration causing erythema or necrosis by intradermal injection into guinea-pigs favoured the diamidines.

Malcolm Woodbine

ANTIBIOTICS

1995. **The Identification of Antibiotics by Means of Resistant Strains of Bacteria**

P. G. STANSLY. *Journal of Bacteriology* [*J. Bact.*] **55**, 721–726, May, 1948. 7 refs.

The author proposes that an agency should be set up for the maintenance of strains of bacteria specifically resistant to known antibiotics. The application of the plan to the identification of new antibiotics would be as follows. Suppose P, R_1, R_2, R_3, R_4 . . . R_n to be the parent strain and strains derived therefrom which are resistant to known antibiotics A_1, A_2, A_3, A_4 . . . A_n and the inhibition ratio, R/P, determined under standard conditions for each of the antibiotics, to be 256, 64, 1024, 512 . . . 128, respectively, also suppose an unidentified antibiotic "X", tested against the parent and resistant strains under similar conditions, to have inhibition ratios of 1, 1, 1, 512. Then a comparison between the ratios for X and the known antibiotics would provide presumptive evidence for the identity of X and A_4 and fairly conclusive evidence that X is not A_1, A_2, or A_3, a difference in inhibition ratios being more significant than a similarity. A number of examples are given for clarification. The possibility of mutation of resistant strains by spontaneous decrease or loss of resistance has been appreciated but since the stability of resistant strains is as yet an unknown factor the author feels that this should not prevent the plan from being tried out.

H. J. Bensted

1996. **Streptomycin. IV. Adsorption of Streptomycin by Susceptible and Resistant Bacteria**

S. BERKMAN, R. J. HENRY, R. D. HOUSEWRIGHT, and J. HENRY. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 65–70, May, 1948. 6 refs.

The authors have shown elsewhere that streptomycin inhibits the carbohydrate metabolism of sensitive strains, but not of resistant strains, of bacteria. They have now attempted to discover whether there is any difference in the adsorption of the antibiotic by resistant and susceptible strains. *Staphylococcus aureus, Shigella dysenteriae*

Sonne, and *Bacillus cereus* were used, the resistant strains being capable of growth in the presence of 1,000 μg. per ml. of streptomycin, and the sensitive strains being inhibited by 1 μg. per ml.

Organisms, grown in brain–heart infusion broth with *p*-aminobenzoic acid at 37° C. for 16 hours and shaken continuously, were separated by centrifuging, washed, and suspended in distilled water to which streptomycin was added. After 2 to 4 hours' shaking at 37° C., the cells were spun down, and the streptomycin in the supernatant solution was assayed. The cells were then eluted by shaking for 24 hours with distilled water, and the streptomycin in the eluate was determined. Resistant and susceptible strains behaved similarly, both adsorbing considerable amounts of antibiotic and reaching equilibrium in three-quarters of an hour; the drug was not readily eluted. The addition of sodium chloride to produce molar concentration greatly reduced the amount of streptomycin adsorbed, and, when this salt was used for elution, the drug was recovered almost quantitatively. This finding is interpreted as indicating that streptomycin is not distributed through the bacterial protoplasm, but is adsorbed upon the cell surface. In order to avoid the errors introduced by the presence of residual supernatant liquid among the centrifuged cells, the desorption of streptomycin was studied by dialysing a suspension of treated bacteria in cellophane bags against water or sodium chloride solution. The streptomycin was steadily desorbed from the organisms. In further experiments, a susceptible strain of *B. cereus* was exposed to streptomycin, diluted, and plated out on nutrient agar. No difference was observed between the rates of growth of treated and untreated bacteria, again indicating that the antibiotic was readily desorbed.

The authors conclude that the persistent action of streptomycin which occurs *in vivo* after the blood concentration has fallen below detectable limits cannot be explained by the slow desorption of the drug from the infecting organisms. [No experiments were made in the presence of plasma proteins.] *L. G. Goodwin*

1997. **Effect of Infused Streptomycin in the Mammary Gland**

C. R. Smith, W. E. Petersen, and R. W. Brown. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 216–219, May, 1948. 3 refs.

A solution containing 20,000 units of streptomycin per ml. in distilled water was infused in doses of 100,000 to 500,000 units per quarter into the udders of 5 normal lactating cows, and in doses of 140,000 or 200,000 units per half-udder in a goat. The animals were milked out completely at intervals, and the streptomycin was determined in the milk by a modified cup-plate method. The concentration of antibiotic found in the milk varied with the dose given and with the milk production of the individual quarter, but did not fall below 20 units per ml. in any sample taken up to 24 hours after the infusion. The concentration in successive samples gradually decreased, but detectable amounts of streptomycin were still present after 48 hours. It is suggested that the drug may be fixed locally in the tissues of the mammary gland, the amount diminishing as each milk sample is equilibrated with the tissues and removed. In the goat and in one of the cows, determination of streptomycin in the urine showed that a steady excretion of 2 to 135 units per ml. took place for at least 32 hours. No streptomycin could be detected in the blood. The treatment caused no irritant effects upon the udder, and the *p*H and chloride content of the milk were unaffected. *L. G. Goodwin*

1998. **Disturbances of Colour Vision and Perspective Due to Streptomycin.** (Poruchy barevného a perspektivního vidění po streptomycinu)

E. Eiselt and A. Kloubek. *Časopis Lékařů Českých* [*Čas. Lék. čes.*] **87**, 549–551, May 7, 1948. 6 refs.

The authors describe unusual toxic symptoms after administration of 2 g. of streptomycin to a patient suffering from a *Bacterium coli* infection of the upper intestinal tract. The patient received by injection 1 g. of streptomycin divided into 8 doses in 24 hours, and in addition 1 g. of streptomycin by a duodenal tube. Soon after the treatment started, the patient became unusually euphoric and complained of disturbances of colour vision and perspective, but these symptoms disappeared after the dose had been reduced to 1 g. daily. The authors diagnosed this case as a mild allergic encephalitis. *J. Ungar*

1999. **Streptomycin in Bubonic Plague**

C. Haddad and A. Valero. *British Medical Journal* [*Brit. med. J.*] **1**, 1026–1027, May 29, 1948. 4 refs.

Seventeen patients with bubonic plague from Haifa and district received hospital treatment in June and July, 1947. Sulphadiazine 2 g., followed by 1 g. 4-hourly, was given as a routine and only 1 patient died. Three others, who were seriously ill on admission, and whose conditions got worse in spite of treatment, which included in 2 cases sulphonamides intravenously, were given streptomycin. They had all been treated by local practitioners for from 3 to 6 days before admission with penicillin and/or sulphathiazole. *Pasteurella pestis* was recovered in each case from buboes. Streptomycin in doses of 200 mg. 3-hourly produced marked improvement within 12 hours in 2 cases, while the third responded to 300 mg. doses within 24 hours. All recovered. Buboes did not resolve, however, and went on to suppuration, requiring incision and drainage. *Clement Chesterman*

2000. **Effect of Streptomycin Aerosol on Friedländer's Pneumonia in Rats**

F. P. Hadley, A. M. Laurent, and J. M. Onslow. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 210–212, May, 1948. 5 refs.

Rats weighing 175 to 250 g. were infected by intrabronchial inoculation with a strain of Friedländer's bacillus in the mucoid phase, suspended in 6% mucin. A dose of 300 organisms (the MLD) caused death in

150 hours, and 30,000,000 organisms (100,000 MLD) killed in 50 hours. A dose of 50,000,000 organisms suspended in broth did not cause death. In infected animals there was consolidation, oedema, and necrosis of the inoculated lobe of the lung, with acute inflammation and exudate around the other lobes. Lung abscess developed in some animals. Within 1 hour to 2 hours of inoculation, groups of 10 rats were placed in a chamber into which a mist of streptomycin in 0·85% saline was introduced. The amount of drug inhaled by each rat during 15 minutes' exposure was estimated to be 1,000 to 2,200 μg., but it is probable that the actual amount was less than this. Four treatments were given at 3-hourly intervals on each of 3 or 4 successive days. Of 30 rats inoculated with 30,000 to 100,000 MLD of bacilli, 60 to 70% survived after treatment; all of 30 control rats died. With a smaller inoculum of 17,000 MLD, all of 10 rats survived and 8 of 10 controls died in 4 days. If the streptomycin was given intramuscularly in doses of 1,000 μg. or 500 μg. at the same time intervals, all of the rats survived. The greater efficacy of intramuscular injection compared with inhalation is thought to be due to the fact that streptomycin, unlike penicillin, is but slowly absorbed from the lung into the blood stream [see Abstract 2005]. The septicaemia which occurs is therefore less well controlled than if the drug is given parenterally. *L. G. Goodwin*

2001. **Grisein, an Antibiotic Produced by Certain Strains of *Streptomyces griseus***
D. M. Reynolds and S. A. Waksman. *Journal of Bacteriology* [*J. Bact.*] **55**, 739–752, May, 1948. 5 figs., 5 refs.

Relatively small numbers of strains of *Streptomyces griseus* produce antibiotics of any kind and the formation of streptomycin is limited to a certain few. Occasionally strains have been isolated which produce other antibiotics. From the culture medium in which one such strain was grown an antibiotic, designated " grisein ", was isolated whose chemical properties and antibacterial spectrum are distinct from those of other well-known antibiotics. This antibiotic develops when *S. griseus* is grown in natural or synthetic fluid media as surface or submerged cultures. In order to eliminate the possibility that streptomycin production by the same strain might influence the estimation of grisein concentration in the metabolite, a streptomycin-resistant strain of *Bacterium coli* is used for assay purposes. The isolation and chemical properties of grisein are described. One of the most important differences between grisein and streptomycin is that the former remains unaffected by sulphhydryl compounds or carbonyl groups. The antibacterial spectrum of grisein has a similar pattern to that of streptomycin and streptothricin but is much narrower. Organisms resistant to these antibiotics may be sensitive to grisein but resistance to grisein appears to be developed more quickly than to streptomycin. The addition of grisein in small amounts to streptomycin solutions has a synergistic effect on organisms sensitive to both substances and appears to retard the development of resistant strains. The fact that grisein is well tolerated by animals and is also active *in vivo* against organisms to which it is sensitive *in vitro* suggests that it may be of value in supplementing streptomycin therapy by suppressing the development of certain strains of coliform bacteria sensitive to its action. *H. J. Bensted*

2002. **Chloromycetin in the Treatment of Patients with Typhus Fever**
J. E. Smadel, A. P. Leon, H. L. Ley, and G. Varela. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 12–19, May, 1948. 6 figs., 5 refs.

On the results obtained in a limited number of cases (12 patients, of which 3 were adults and the remainder children), it is concluded that chloromycetin is relatively safe in the dosage employed; the results were sufficiently encouraging to warrant further clinical trials. The adult dose (the dose given to children was based on body weight), was 1 to 2 g. initially by mouth followed by daily doses of 0·2 g. 4-hourly (1 g. daily) for periods varying from 4 to 14 days. A recommended initial dose is 40 mg. per kilo body weight, followed by a total daily dose of 35 mg. per kilo until obvious improvement in the patient's condition is noted. Subsequently a daily maintenance dose of 20 mg. per kilo can be given until the fourteenth day. The course of the disease was followed by specific rickettsial complement-fixation and agglutination tests, as well as by the Weil–Felix test. The cases included both murine and epidemic types of typhus. The improvement, if any, was not observed until the seventh or eleventh day of treatment. *R. Wien*

2003. **Administration of Chloromycetin to Normal Human Subjects**
H. L. Ley, J. E. Smadel, and T. T. Crocker. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 9–12, May, 1948. 2 figs., 4 refs.

Two normal male subjects received a prolonged course of chloromycetin beginning with a single dose of 1 g., followed by 1 g. daily (divided into 0·2 g. doses 4-hourly) for 10 days. The amounts of the drug in blood and urine were determined by a method in which the inhibition by the antibiotic of the growth of *Shigella sonnei* is measured. Maximum levels of 5 to 10 μg. per ml. were obtained in blood within 2 hours of the initial dose, this level falling rapidly until none was detectable at 8 hours. Maximum levels in urine of about 200 μg. per ml. were obtained. *R. Wien*

2004. **Tuberculostatic Action of Chloromycetin *in vitro* and *in vivo***
G. P. Youmans, A. S. Youmans, and R. R. Osborne. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **67**, 426–429, April, 1948. 8 refs.

Chloromycetin, the antirickettsial antibiotic isolated from a *Streptomyces* species, was moderately tuberculostatic *in vitro*. Sub-surface growth of most strains of

human-type tubercle bacilli, at a concentration of 0·01 mg. per ml. in Youmans's synthetic medium, was completely inhibited by the antibiotic at concentrations of 6 to 12 μg. per ml. in the presence of 10% of serum, compared with less than 1 or 2 μg. per ml. of streptomycin or of *p*-aminosalicylic acid (PAS). Activity was much less affected by increasing the inoculum of bacilli than in the case of PAS. The bacteriostatic action of streptomycin or PAS was not improved by the addition of chloromycetin *in vitro*. *In vitro* tests in experimental tuberculosis in mice failed to reveal chemotherapeutic action when chloromycetin was injected subcutaneously (in 20% aqueous propylene glycol). Oral administration, however, at 0·5% and 0·25% of the diet, increased survival time; while there was little difference from the untreated controls in the amount of gross pulmonary disease at death or on termination of the experiment, microscopical examination revealed a greater tendency to proliferative-type lesions in the drug-treated groups. The authors conclude that chloromycetin is "slightly effective for the suppression of experimental tuberculosis". *P. D'Arcy Hart*

PENICILLIN

2005. **Penicillin and Streptomycin in Lungs and Blood Serum of Rats Following Inhalational and Intramuscular Administration**

A. M. Laurent, A. P. McIlroy, and F. P. Hadley. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 213–216, May, 1948. 2 figs., 8 refs.

Groups of 10 rats weighing 250 g. were treated with penicillin or streptomycin either by intramuscular injection or by exposure for 15 minutes to an atmosphere containing mist from a solution of the drug in saline. At intervals, pairs of rats from each group were anaesthetized with ether and bled from the heart, the serum being separated. The lungs were removed aseptically, freed from blood, ground with sand and 1·5 ml. of saline, and centrifuged. The concentrations of antibiotic in the serum and lung extract from each animal were determined by the activity against broth cultures of a haemolytic streptococcus (penicillin) or Friedländer's bacillus (streptomycin).

After the inhalation of a dose of 2,000 units of penicillin the lungs contained a much higher concentration than that produced by 5,000 units given intramuscularly. The level was maintained for 1 hour, and penicillin could still be detected in the lung after 2 hours. In the serum the concentration attained immediately after inhalation was 0·33 unit per ml., falling to 0·04 unit per ml. in 1 hour. The corresponding concentrations after intramuscular injection of 2,000 units were 0·6 unit per ml. and 0·04 unit per ml. respectively. Penicillin was therefore readily absorbed into the blood stream after inhalation. After the inhalation of a dose of 2,300 μg. of streptomycin, the amount of drug in the lungs remained large for 3 hours. In spite of this, the concentration in the serum never reached 1 μg. per ml., showing that streptomycin is poorly absorbed from the lung into the blood. Intramuscular injection of 2,500 μg. gave a serum level of 15 μg. per ml. decreasing to 1 μg. per ml. in 3 hours; the lungs contained only about one-quarter of the quantity found after inhalation. *L. G. Goodwin*

2006. **Dynamics of the Action of Penicillin. Time–Dose Relationship in Human Streptococcic Disease**

E. Jawetz. *Archives of Internal Medicine* [*Arch. intern. Med.*] **81**, 203–208, Feb., 1948. 11 refs.

Penicillin G was administered by injection to 81 patients with streptococcal sore throat. Satisfactory clinical and bacteriological results were obtained with small doses given frequently (10,000 units 3-hourly) as with larger doses given at longer intervals (150,000 units 12-hourly), provided that they were continued for not less than 4 days. [The nature of the penicillin vehicle is not disclosed, but it has been assumed to be aqueous.]

J. E. M. Whitehead

2007. **Oral Penicillin in the Treatment of Various Bacterial Infections**

J. A. Robinson, H. L. Hirsh, and H. F. Dowling. *American Journal of Medicine* [*Amer. J. Med.*] **4**, 716–723, May, 1948. 53 refs.

Penicillin tablets (sodium salt) buffered with calcium carbonate were administered orally in the treatment of various bacterial infections [strength of each tablet not given]. In all infections, except subacute bacterial endocarditis in which oral penicillin is not recommended because of the seriousness of the disease, the results were comparable with those obtained with parenteral penicillin. The total oral dose of penicillin was 5 times higher than the total intramuscular dose for the same infection. Toxic effects were less often observed with oral therapy, the results of which are tabulated as follows:

Disease	Recovered	Unimproved	Died	Dosage-schedule
Pneumococcal pneumonia	109	—	4	75,000 units every 3 hours until afebrile for 48 to 72 hours.
Scarlet fever ..	94	—	0	125,000 units every 3 hours for 5 days.
Tonsillitis and pharyngitis.	38	0	—	100,000 to 125,000 units every 3 hours for 5 days.
Erysipelas ..	6	—	0	100,000 to 125,000 units every 3 hours for 5 days.
Otitis media ..	16	1	—	100,000 to 125,000 units every 3 hours for 48 hours after all evidence of active infection has disappeared.
Vincent's angina	6	0	—	50,000 to 75,000 units every 2–3 hours for 3 to 4 days.
Infections of the skin	21	1	—	125,000 units every 3 hours for 5 days.
Bacterial endocarditis	0	2	—	Oral penicillin not recommended.
Total ..	290	4	4	

Death occurred in 4 cases of pneumonia. Two patients were moribund on admission and died in a few hours. One had diffuse bronchopneumonia and fibrinous

pericarditis and died 39 hours after treatment was started. The fourth case was in a woman of 98 who died of intestinal haemorrhage.

[These figures are very impressive and the simplicity of oral therapy makes it a very desirable method of administering penicillin which should receive wider study.]

S. Karani

2008. **Changes in the Bacterial Flora of the Throat and Intestinal Tract During Prolonged Oral Administration of Penicillin**

M. O. LIPMAN, J. A. COSS, and R. H. BOOTS. *American Journal of Medicine* [*Amer. J. Med.*] **4**, 702–709, May, 1948. 6 refs.

The authors record their observations on changes in the normal bacterial flora of throat and intestinal tract during and after oral administration of amorphous penicillin (sodium salt). They selected 10 patients with rheumatoid arthritis, of different ages, attending the Arthritic Clinic of the Presbyterian Hospital, Columbia University, New York. Each adult received 1,000,000 units and each child 500,000 units of penicillin a day for a prolonged period [exact duration of treatment not stated]. Morphological, biochemical, and serological studies of the organisms obtained from the throat and stool were made before, during, and after penicillin therapy and the following observations are recorded: (*a*) Bacterial flora of the throat consisting of predominantly Gram-positive cocci before treatment became predominantly Gram-negative during treatment, and cessation of therapy produced rapid reappearance of Gram-positive organisms. Gram-negative coliform bacillus were observed during treatment only. (*b*) Bacterial flora of the intestinal tract showed no significant change in the character of the organisms. The only change observed was a lower incidence of streptococcus-positive stool cultures during treatment, compared with periods before or after penicillin therapy. The authors also studied the penicillin-sensitivity of these organisms; there was no evidence to show that bacterial resistance to penicillin developed during the prolonged therapy. The effect of penicillin therapy on rheumatoid arthritis is not discussed.

S. Karani

2009. **Fate and Distribution of Penicillin in the Body. I. Circulation of Penicillin in the Lymph**

R. J. SCHACHTER. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 29–34, May, 1948. 3 figs., 8 refs.

Experiments on 23 dogs were undertaken to determine the concentration of penicillin in the lymph in relation to that in the blood, since it was thought that this might throw light on its fate in the body, the drug being retained in the tissues and urine long after its disappearance from the blood stream. Lymph was obtained from a cannula tied into the thoracic duct in anaesthetized animals, After intravenous or intramuscular injection of 20,000 i.u. of penicillin it was retained longer in the lymph than in the blood. For example, after intravenous injection, the level in serum after 3 hours was 0·125 unit per ml. and at 4 hours none was detectable; in lymph the levels were 0·25, 0·125, 0·06, and 0·03 unit per ml. at 3, 4, 5, and 6 hours respectively. A bacteriostatic level appeared earlier in blood than in lymph. The penicillin concentrations in the liver and kidneys closely followed those in lymph. Similar results were obtained after the intramuscular injection of penicillin in oil. The appearance of penicillin in the blood earlier than in the lymph suggested that the absorption of penicillin takes place through the blood capillaries. The prolongation of the presence of penicillin in the lymph is of interest, considering the part played by the lymphatics in certain infections.

R. Wien

2010. **Penicillin in the Cerebrospinal Fluid Following Parenteral Penicillin**

W. P. BOGER, R. B. BAKER, and W. W. WILSON. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 101–106, May, 1948. 2 figs., 26 refs.

Twenty-six patients suffering from syphilis of the central nervous system (paresis) were treated with 100,000 units of penicillin intramuscularly every 3 hours for 3 days, followed by the same dose of penicillin together with 3 g. of caronamide (4′-carboxyphenylmethane sulphonanilide) orally every 3 hours for a further 5 days. Caronamide was given since it inhibits excretion of penicillin by the renal tubules, yielding higher concentrations of penicillin in the plasma. After the 5 days of the penicillin therapy alone, in 15 patients the levels in the cerebrospinal fluid ranged from 0·019 to 0·052 unit per ml. At the end of the further period of 5 days (during which caronamide was given as well), in 20 patients concentrations of penicillin in the cerebrospinal fluid ranged from 0·026 to 2·5 unit per ml. The levels obtained were considered to be therapeutically significant since a concentration of 0·03 unit per ml. is usually sufficient to inhibit the growth of organisms such as streptococci, meningococci, and staphylococci. A lengthy discussion is given on the penetration of penicillin through the blood–brain barrier.

R. Wien

2011. **Cytochemical Mechanisms of Penicillin Action. VI. The Influence of Cobalt on the Optimal Bacteriostatic Concentration of Penicillin**

R. PRATT and J. DUFRENOY. *Journal of Bacteriology* [*J. Bact.*] **55**, 727–738, May, 1948. 5 figs., 29 refs.

Previous papers by these authors have drawn attention to the enhancement of the antibacterial action of penicillin by the addition of low concentrations of cobalt which do not by themselves inhibit multiplication of the organism under test. This work has been extended and the question of optimal concentration of penicillin has also been examined.

Organisms depending for their survival on the absorption of glutamic acid from the substrate are penicillin-sensitive. This and similar observations suggest that the effect of penicillin may be traceable ultimately to dehydrogenation of reduced glutathione to oxidized glutathione resulting largely from the increased metabolic

rate induced by appropriately low concentrations of penicillin. The most effective bacteriostatic concentration of the drug would then be one that promotes dehydrogenation faster than rehydrogenation can restore the —SH groups, and this would be the minimal concentration capable of inducing irreversible injury to the bacterial cells.

The threshold concentration of penicillin required to check the growth of *Staphylococcus aureus* in serial dilutions was found to be 0·01 unit per ml., but when the broth contained 1 mg. cobalt chloride per litre the threshold value was 0·001 unit per ml. It is submitted that the effectiveness of cobalt in lowering this threshold is due to the accelerated formation of complexes involving sulphhydryl groups. The irreversible change which occurs when the penicillin concentration is optimal is associated with changes in the morphology of the bacterial cells and their reaction to vital stains. These morphological changes do not occur when the concentration of penicillin is increased significantly.

H. J. Bensted

2012. **Local Penicillin Therapy with "Peniciplast".** (Zur lokalen Penicillin-Therapie mit Peniciplast)
O. HASLAUER. *Wiener Klinische Wochenschrift* [*Wien. klin. Wschr.*] **60**, 331–333, May 28, 1948. 32 refs.

Owing to the shortage of penicillin in Austria a local product named "peniciplast" has been used in 139 cases of purulent inflammations and in 11 cases with recent wounds. Peniciplast consists of an actively growing and penicillin-producing strain of *Penicillium notatum* on an agar substrate containing several nutrient substances not further defined. This preparation is stated to contain about 10,000 units of unpurified penicillin. It has been applied as a local dressing, the lower surface of the agar preparation being applied directly to the lesions. These dressings were changed at least every 48 hours. Out of a total of 150 cases 6 were treated unsuccessfully. Two of these were cases of osteomyelitis of the finger phalanx, 2 were cases of carbuncles due to penicillin-resistant or penicillinase-forming micro-organisms, and 2 were cases of varicose ulcers in which failure was ascribed to poor local circulation.

K. S. Zinnemann

2013. **Evidence for an Electrostatic Field on Penicillin Assay Plates**
J. DUFRENOY and R. PRATT. *Nature* [*Nature, Lond.*] **161**, 849–850, May 29, 1948. 1 fig., 9 refs.

When bacteria are lysed changes in electric charge occur. These changes in electric charge can be demonstrated on penicillin assay plates by treatment with electronegative or electropositive colloids suspended in buffers at *p*H levels above or below the isoelectric range of the nucleoproteins present. When bacteria are lysed by penicillin there is increased electronegativity in the regions of enhanced growth and increase of positive charges in the zones of inhibition, no similar changes are seen on unseeded plates exposed to penicillin.

G. M. Findlay

2014. **Stabilization of Penicillin-salt Solutions with Sodium Citrate.** [In English]
L. HAHN. *Biochimica et Biophysica Acta* [*Biochim. biophys. Acta, Amst.*] **2**, 113–120, March, 1948. 1 fig., 7 refs.

The author has previously shown (*Lancet*, 1947, **252**, 408) that a concentration of one three-hundredth molar to one four-hundredth molar sodium citrate in 0·9% sodium chloride has an optimum stabilizing effect on solutions containing 5 units per ml. of sodium penicillin. Although the stability of penicillin salts in aqueous solution is conditioned by such factors as *p*H, temperature, purity, salt concentration, and the addition of buffers, the author shows that the stability conferred by citrate is maintained in the much higher concentrations of sodium and calcium penicillins used in clinical treatment. Such solutions can be sterilized in ampoules and subsequently maintained at room temperature; solutions of 5,000 units of penicillin per ml. in one-fortieth molar sodium citrate in 0·9% sodium chloride were kept for 15 minutes at 100° C. and the ampoules then maintained at room temperature; 80% of the penicillin was still present after 25 days.

Malcolm Woodbine

2015. **Enhancement of Penicillin Effectiveness by Traces of Cobalt**
L. A. STRAIT, J. DUFRENOY, and R. PRATT. *Journal of the American Pharmaceutical Association, Scientific Edition* [*J. Amer. pharm. Ass., Sci. ed.*] **37**, 133–135, April, 1948. 1 fig., 9 refs.

The addition of traces of cobalt ($CoCl_2.6H_2O$) in a concentration of 0·1 to 10 parts per million to the agar plates in the assay of penicillin (crystalline penicillin of potency 1,560 units per mg.) produced a marked increase in the diameters of the zones of inhibition. This result was obtained with *Staphylococcus aureus*, *Bacterium coli*, *Proteus vulgaris*, and *Bacillus subtilis*. The effect of cobalt was to increase the potency assay of penicillin 2 to 4 times. These results were obtained after short periods of incubation (2 to 3 hours). Of equal interest was the effect on a penicillin-resistant organism, *Bact. coli*. On agar plates infected with *Bact. coli*, 10 units per ml. of penicillin was required to produce zones of inhibition of about 12 mm. diameter, whereas with the addition of only 0·1 mg. per litre of cobalt chloride (0·1 part per million) only 1 unit per ml. of penicillin was required to produce zones of inhibition of the same size. It is suggested that the effect of cobalt may be due in some measure to a stimulation of the growth of bacteria, rendering them more susceptible to the action of penicillin while in the logarithmic phase of growth.

R. Wien

2016. **Quantitative Sensitisation of a Penicillin-resistant Staphylococcus**
H. I. WINNER. *Lancet* [*Lancet*] **1**, 674, May 1, 1948. 1 fig.

The author has confirmed a previous report (Voureka, *Lancet*, 1948, **1**, 62) that penicillin-resistant organisms can

be rendered sensitive by growing them in contact with penicillin-sensitive organisms. A resistant strain of *Staphylococcus aureus* developed sensitivity after incubation in broth for 4 hours with a penicillin-sensitive strain of *Streptococcus pyogenes*. By growing the staphylococcus before and after sensitization in the presence o f varying concentrations of penicillin it was shown that its sensitivity had been increased 200 times. No further increase of sensitivity could be produced when the sensitized staphylococcus was incubated with *Strep. pyogenes* for a further period of 4 hours. It was also observed that the sensitizing strain of streptococcus became resistant to penicillin after incubation with the original resistant strain of staphylococcus.

D. J. Bauer

2017. **Significance of the Gram Test for Bacteria in Relation to Penicillin Bacteriostasis**
M. GEORGE and K. M. PANDALAI. *British Medical Journal* [*Brit. med. J.*] **1**, 1028–1029, May 29, 1948. 7 refs.

Following on their work on the influence of nucleic acids on penicillin bacteriostasis of Gram-positive organisms (*Brit. med. J.*, 1947, **2**, 210), these authors now report the effect of added magnesium ribonucleate on the growth of Gram-negative organisms (*Bacterium coli*) when the latter are in contact with penicillin. Magnesium ribonucleate alone cannot convert Gram-negative bacilli into Gram-positive bacilli and cannot increase the penicillin-sensitivity of relatively insensitive organisms; indeed their resistance is increased. The authors find, however, that magnesium ions, quite apart from the ribonucleate moiety, do exert a favourable influence on the inhibitory power of penicillin on the growth of *Bact. coli*. The presence of 0·1% magnesium sulphate reduced the bacteriostatic dose of penicillin from 12 units per ml. to about 8 units per ml.

H. J. Bensted

2018. **Mechanism of the Topical Effect of Penicillin G in Experimental Local Streptococcal Infections**
E. GRUNBERG, R. J. SCHNITZER, and C. UNGER. *Yale Journal of Biology and Medicine* [*Yale J. Biol. Med.*] **20**, 479–486, May, 1948. 7 refs.

Mice were inoculated subcutaneously with penicillin G and group B streptococci. The site of infection became sterile between 5 and 6 hours after inoculation, yet penicillin was no longer detectable in any quantities in the subcutaneous tissue after about 2 hours. The authors explain this discrepancy by the assumption that the organisms are irreversibly damaged during the first hours, and that these damaged cocci are subsequently destroyed by the defence mechanism of the host.

R. Salm

2019. **Dermatitis Due to the Preparation and Administration of Penicillin Solution**
W. C. MARCH and W. N. NEW. *United States Naval Medical Bulletin* [*Nav. med. Bull., Wash.*] **48**, 391–394, May–June, 1948. 2 figs., 4 refs.

SULPHONAMIDES

2020. **Sulphanilamide Inhibition of Carbonic Anhydrase in Whole Blood**
D. J. ANDERSON and L. C. THOMSON. *Journal of Physiology* [*J. Physiol.*] **107**, 203–209, March 15, 1948. 1 fig., 9 refs.

Blood was withdrawn from volunteers in such a manner that it could be kept under a paraffin seal as soon as it was taken from the vein. The blood was then exposed to air by allowing it to drop through wide tubes of either 8 or 30 ft. (2·4 or 9 m.) in length. Plasma CO_2 concentration was measured before and after the exposure to air, and the difference was used as a measure of the CO_2 loss.

It was found that the addition of concentrations of sulphanilamide of over 50 mg. per 100 ml. caused a delay in the liberation of CO_2. This was probably due to an inhibition of the enzyme carbonic anhydrase. This effect is probably negligible with therapeutic concentrations of sulphanilamide—that is, up to 10 to 15 mg. per 100 ml. of blood.

G. A. H. Buttle

2021. **Protective Action of Methionine Against the Thyroid Hyperplasia due to the Action of Sulphonamides.** (Action protectrice de la méthionine à l'égard de l'hyperplasie thyroïdienne d'origine sulfamidique)
A. ASCHKENASY, G.-J. ROLLAND, and C. POLONOVSKI. *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences* [*C.R. Acad. Sci., Paris*] **226**, 1757–1759, May 24, 1948. 2 figs.

The bacteriostatic action of sulphonamides is inhibited by methionine. When 0·4% of sulphadiazine is added to the diet of rats goitre results, but if 0·3% *dl*-methionine is given the action of sulphadiazine on the thyroid gland is no longer seen. In rats fed on sulphadiazine alone the thyroid was greatly hypertrophied with very little colloid; when methionine was added the thyroid was normal in appearance. The mechanism by which methionine inhibits the goitrogenic action of sulphadiazine is unknown.

G. M. Findlay

2022. **Production of Aminobenzoic Acids by Bacteria Resistant to Sulphonamides**
R. LEMBERG, J. P. CALLAGHAN, D. E. TANDY, and N. E. GOLDSWORTHY. *Australian Journal of Experimental Biology and Medical Science* [*Aust. J. exp. Biol. med. Sci.*] **26**, 9–27, Jan., 1948. 24 refs.

The authors, working in the Institute of Medical Research of the Sydney Royal North Shore Hospital, have attempted to elucidate the phenomena of natural and acquired drug-resistance by investigations on a strain of *Bacterium coli commune*, with particular reference to the production of *p*-aminobenzoic acid by the organism. Attempts were made to develop a method of extraction and separation of aromatic amino-acids sufficiently sensitive for the low concentrations found in bacterial cultures, and the method adopted was to transform the acids into azo-dyes by diazotising and coupling with

dimethyl-α-naphthylamine, to separate the acid from the non-acid dyes, and to separate the acid dyes by chromatography. The experiments were carried out with small inocula of some 1,000 organisms per ml., a basal synthetic medium, and sodium sulphathiazole for inculcating sulphonamide resistance.

The strain of *Bact. coli* produced diazotisable amino-acids in the supernatant, the major portion being anthranilic acid with only a small amount of *p*-aminobenzoic acid after adaptation to the sulphathiazole; no more *p*-aminobenzoic acid was produced than with the parent susceptible strain. Further, the amount of *p*-aminobenzoic acid was insufficient to account for resistance to the sulphathiazole—and this held for the sum of *o*- and *p*-aminobenzoic acids produced. The production of anthranilic acid was variable and decreased with the number of subcultures.

The authors conclude that *p*-aminobenzoic acid production cannot be invoked to explain the drug-resistance of *Bact. coli* and that if the Woods–Fildes theory, that an enzyme operating on *p*-aminobenzoic acid as substrate is inhibited competitively by sulphonamides, is to be retained then drug-resistance must be interpreted as due to the development of an alternative metabolic mechanism by the organism. While admitting that there is no evidence that the same mechanism applies to all organisms, the authors point out that failure to produce an increase in *p*-aminobenzoic acid by one necessitates a full investigation of other organisms. *Malcolm Woodbine*

2023. **Investigation of Some Newer Sulfonamides as Intestinal Chemotherapeutic Agents**
H. J. Florestano and M. E. Bahler. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **92**, 196–206, Feb., 1948. 1 fig., 23 refs.

Preliminary chemotherapeutic studies of 2-sulphanilamido-5-carbamylthiazole (SC), 2-(N^4-succinamylsulphanilamido)-thiazole (ST), and 2-(N^4-succinylsulphanilamido)-1,3,4-thiadiazole (SD) are described. SC differs from sulphathiazole in having a carbamyl group in the 5 position, a substitution which markedly reduced the blood concentrations in mice after single oral doses of 1 g. per kg., compared with sulphathiazole. Its marked antibacterial action against coliform organisms in mice and dogs is apparently due to the drug itself, since the latter is stable to autoclaving. ST differs from succinylsulphathiazole in the replacement of a carboxy group with a carbamyl group, resulting in a more easily hydrolysed drug. Blood concentrations after administration of 1 g. per kg. orally to mice and dogs were low compared with those of succinylsulphathiazole but the drug was only about a third as effective in reducing the coliform counts of faeces of groups of mice given 2·2 g. per kg. daily.

The compound SD is a succinyl derivative of sulphathiadiazole, less well absorbed than " sulphathalidine " in mice and dogs given 1 g. per kg., although there appears to be less free drug (SD) in dog faeces. Anti-coliform activity of SD, compared with that of sulphathalidine, was greater in mice and the same in dogs.
George Brownlee

2024. **A Clinical Evaluation of a Recent Sulfonamide: Nu-445**
R. S. Rodgers and F. H. Colby. *Journal of Urology* [*J. Urol.*] **59**, 659–663, April, 1948. 2 refs.

The new sulphonamide, " Nu-445 " is 3,4-dimethyl-5-sulphanilamido-*iso*xazole. The authors have used this compound in 20 cases of urinary infection caused by various Gram-negative organisms, chiefly *Bacterium coli*, *Proteus vulgaris*, and *Pseudomonas pyocyanea*. By *in vitro* experiments, they found that the drug was most effective at a *p*H of between 7·0 and 8·0. The urine of all patients was therefore rendered alkaline during the treatment by the administration of sodium citrate. The usual daily dose of Nu-445 was 4 g., but some patients received 8 g. and others even 12 g. daily. There was no response in 13 cases, but 7 showed definite improvement. There appeared to be no relation between the levels of the drug in blood or urine and the clinical results. Some of the good results were observed in patients receiving the smaller dose. In none of the cases was there any complicating factor such as a foreign body or an inlying catheter. Crystalluria did not occur. In 3 cases the treatment had to be stopped because of toxic symptoms.
Thomas Moore

TOXICOLOGY

2025. **Influence of BAL on the Toxicity and Chemotherapeutic Activity of Mapharsen**
N. Ercoli and W. Wilson. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **92**, 121–126, Feb., 1948. 9 refs.

Albino mice (weighing 18 to 30 g.) infected intraperitoneally with 0·5 ml. of a suspension containing 10 *Trypanosoma equiperdum* per microscope field (×400 magnification) die within 3 to 4 days. A single subcutaneous dose of 5 mg. " mapharsen " per kg. given after 44 to 48 hours sterilized 71% of mice; doses of 1·2 mg. per kg. are trypanocidal, but relapses occur. As little BAL as one-eighth to one-half the weight of mapharsen will interfere with the sterilizing dose, while as much BAL as 1 to 2·7 times the mapharsen dose is needed to cause loss of trypanocidal activity. It is possible that BAL mobilizes in the first hour after injection the arsenic in the blood and aids its rapid excretion, thus retaining the therapeutic effect but decreasing the curative action. Further, the therapeutic effect in trypanosome infection is accompanied by immune reactions.
George Brownlee

2026. **The Inhibition of Thiol Enzymes by Lachrymators**
J. F. Mackworth. *Biochemical Journal* [*Biochem. J.*] **42**, 82–90, 1948. 8 figs., 21 refs.

This interesting paper deals with fundamental investigations into the mode of action of lacrimators carried out in 1941 in the Biochemical Department of the University of Cambridge. The author shows that various lacrimators inhibit all the enzymes which are generally accepted as thiol enzymes. Inhibition is progressive and irreversible

except in the case of the action of chloropicrin on yeast. The enzymes can be protected by reduced glutathione, cysteine, or denatured enzyme. Lacrimators also inhibit the respiration of muscle and the fermentation and respiration of glucose by yeast. It is suggested that they act like iodoacetate in that they combine irreversibly with thiol groups in the enzyme, but they are much more powerful than iodoacetate. [The vast amount of technical information cannot be abstracted satisfactorily and the interested reader is recommended to consult the original paper.] *G. R. Cameron*

2027. **The Metabolism of the Lungs from Normal Mice and from Mice Exposed to Phosgene**
E. BOYLAND and F. F. MCDONALD. *Biochemical Journal* [*Biochem. J.*] **42**, 68–71, 1948. 3 refs.

The lungs of young adult mice are sufficiently small to allow of measurement of metabolism in the Warburg apparatus without mincing. Mean values of 7·3 for Qo_2 and 3·0 for Q_GN_2 were found. No great changes in the lung metabolism were observed in mice exposed to phosgene. It is therefore unlikely that phosgene oedema of the lungs is due to poisoning of enzymes concerned with glycolysis or respiration in the lungs.
G. R. Cameron

2028. **Studies on Experimental Phosgene Poisoning. V. Infusions in the Treatment of Experimental Phosgene Poisoning**
H. D. BRUNER, M. H. GIBBON, M. D. MCCARTHY, R. D. BOCHE, T. R. TALBOT, J. S. LOCKWOOD, and G. B. SANDERS. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 1125–1131, June, 1948. 15 refs.

In phosgene poisoning the transudation of plasma into the pulmonary alveoli leads to two functional derangements, either of which is potentially lethal. One is the obstruction to pulmonary gaseous exchange due to the physical presence of this fluid in the alveoli and eventually in the bronchioles; the development and magnitude of this lesion can be evaluated by observing the arterial oxygen saturation. The second is loss of circulating plasma volume which results in a state very similar to secondary or surgical shock. On the whole, as is very clearly pointed out in the present paper, attempts to control the haemoconcentration and to restore the plasma volume by infusions sometimes aggravate the double lesion either temporarily or fatally. *G. F. Walker*

2029. **Ethylene Glycol Poisoning. A Clinical and Pathological Study of Three Cases**
P. O. HAGEMANN and T. R. CHIFFELLE. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 573–584, May, 1948. 7 figs., 18 refs.

Ethylene glycol ($HOCH_2CH_2OH$) is used in anti-freeze mixtures and is highly toxic when ingested—much more so than propylene or diethylene glycol. *In vivo* it is oxidized to oxalic acid and then to glycollic acid. Three cases of fatal poisoning with ethylene glycol are described. They were investigated in the Washington School of Medicine, the Barnes Hospital, St. Louis, and Yale University. Full pathological details, with photomicrographs, are given. All were characterized by coma, acidosis, convulsions, and death within 24 hours of drinking ethylene glycol. The actual quantities drunk were not determinable. The primary lesion in these cases was widespread capillary damage. Haemorrhages in pleura, lung, heart, pericardium, kidney, and brain were found. Oedema and fatty infiltration were present in the liver, and calcium oxalate crystals were found in the kidney tubules and brain. Ethylene glycol was widely distributed in the body tissues and urine (the analytical technique is described in detail). Formaldehyde was also detected in small quantities in the urine. Whether death results from chemical meningitis or oxalate poisoning has been controversial. The authors feel that oxalate formation is comparatively unimportant in these cases. Treatment was unavailing. Measures tried included gastric lavage and liberal administration of alkalis and fluids, sodium lactate, magnesium sulphate (for convulsions), and oxygen. *T. E. Graham*

2030. **The Comparative Toxicity of Cryolite for Rats and for Rabbits**
E. J. LARGENT. *Journal of Industrial Hygiene and Toxicology* [*J. industr. Hyg.*] **30**, 92–97, March, 1948. 1 fig., 4 refs.

Previous investigators have obtained contradictory evidence on the toxicity of cryolite for different animals. In the present investigation the effects of natural cryolite and synthetic cryolite were compared, and the rate of elimination of natural cryolite was determined. Aqueous suspensions of cryolite were introduced into the stomach of rats through a blunt metal tube, and into the stomach of rabbits through a rubber catheter. Rats were found to survive exceedingly large doses (up to 80 g. per kg.) of natural and of synthetic cryolite. This must have been due to the rapid elimination of the cryolite from the digestive tract. On the other hand, rabbits were killed by the administration of 9 to 12 g. per kilo of cryolite; this seems to have been due to partial retention of the cryolite for a much longer period within the gastro-intestinal tract. The concentrations of fluoride in the blood of rats to which 16 g. per kg. of cryolite had been administered were much lower than those found in the blood of rabbits given either cryolite or sodium fluoride. Observations suggested that synthetic cryolite may be slightly more toxic than the natural mineral. *H. M. Vernon*

2031. **Methyl Bromide Poisoning.** (L'intoxication par le bromure de méthyle)
J. DECHAUME, L. BOURRAT, B. SCHOTT, and —. BUFFARD. *Journal de Médecine de Lyon* [*J. Méd. Lyon*] **29**, 297–305, May 5, 1948.

Six cases of methyl bromide poisoning were observed by the authors. A study of these cases suggests that the poison takes particular effect on the upper cerebellar peduncles, the red and dentate nuclei, and the corpus striatum. The odour is not strong, so that inhalation

may occur without the victim's knowledge. Symptoms may develop from 1 month to 7 months after exposure has ceased, but more acute illness may develop within 2 days. Prodromal symptoms are usual. These are headache, nausea, vertigo, tremors, and painful hyperacusis. Dysarthria occurs with distortion of the peri-buccal musculature. In graver cases the cerebellar and labyrinthine symptoms are more evident. There may be somnolence, confusion, or coma or depression. Motor symptoms are rare, the pyramidal cortex generally escaping. There may be tremors and myoclonic movements. It is stated that there are no special methods of investigation which throw light on the presence of this form of poisoning. Some of the cases recorded resembled those due to Kojévnikov's syndrome (epilepsia partialis continua). The later the onset of symptoms the less acute the course and the better the chance of recovery. Symptoms may persist for from 12 to 15 months. Death is generally confined to acute cases.

Although adrenaline is suggested in treatment to lessen cerebral capillary vasodilatation, it does not seem to be of much benefit. The intractable myoclonias present a problem, though hyoscine therapy is said by some to be valuable. Prophylaxis lies in strict control in the construction and manipulation of apparatus.

G. C. Pether

2032. **Emetine Toxicity in Man: Studies on the Nature of Early Toxic Manifestations, their Relation to the Dose Level, and their Significance in Determining Safe Dosage**
G. KLATSKIN and H. FRIEDMAN. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 892–915, May, 1948. 2 figs., 55 refs.

This article places upon a sound scientific foundation with a superstructure of careful clinical observation the whole subject of emetine toxicity in man.

Emetine has a selective toxic action upon muscle and accordingly groups of manifestations may be observed in the skeletal muscles, in the alimentary tract, in the heart, and in the nerve-muscle end-plates. Clinically the toxic phenomena are well recognized and understood. Diarrhoea is extremely common and is due to increased peristalsis. Nausea and vomiting may be similarly caused, although it is believed that both are central in origin. Depressive changes in the myocardium can easily be demonstrated in a large proportion of cases by serial electrocardiographic studies. So-called emetine " neuritis " is really a myositis and may be very troublesome. Curiously enough, some of the toxic manifestations of emetine subside with more intensive administration, but this does not apply to myocarditis and myositis. If either of these develop the drug must be stopped forthwith. For the same reason, after a course of emetine, patients should be kept under electrocardiographic, and general clinical, observation because sometimes the toxic action of emetine is strikingly delayed.

[The lesson of this lengthy and valuable paper would appear to be that emetine has a wide range of toxic effects, but these can be avoided by giving it in carefully controlled courses, in full doses with substantial rest periods.]

G. F. Walker

BLOOD TRANSFUSION

2033. **Prothrombin Activity of " Stored Human Blood "**
F. J. SCHILLING, A. DE NATALE, and L. A. AMILL. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 415–418, April, 1948. 2 figs., 19 refs.

A study is described of prothrombin activity in 50 different samples of stored human blood selected at random. In each case 500 ml. of blood was withdrawn and mixed with 125 ml. of acid–citrate–dextrose solution and the resultant mixture examined daily for 21 days. The technique of the Link–Shapiro modification of Quick's method, with rabbit lung as the source of thromboplastin, was followed. For further technical details the original paper should be consulted.

The authors conclude that prothrombin activity or rate of prothrombin conversion in stored blood is increased during the first 4 to 5 days and is normal from the fifth to the seventh day. They suggest that the increased prothrombin activity during the first few days of storage is probably due to the disintegration of platelets, which liberate thromboplastin. Thereafter the prothrombin activity slowly falls to 47·7% by the twenty-first day. They therefore consider that stored blood can be used with success during the first week of storage in the treatment of hypoprothrombinaemia.

Janet Vaughan

2034. **Isoimmunization with the A and B Factors and its Relation to Hemolytic Disease of the Newborn**
S. H. POLAYES and J. MCNALLY. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **18**, 375–386, May, 1948. 4 figs., 16 refs.

The effect of heterospecific pregnancy on anti-A and anti-B agglutinin titre in mothers was studied in 259 women and children. The authors state: " The results seem to indicate that gestation, particularly when it is heterospecific, is associated with an increase in the isohaemagglutinin titre, as compared to the titres found in children and in multigravidas and primiparas with compatible pregnancies ". Four babies with conditions simulating erythroblastosis foetalis were also studied; the authors state that the Rh and Hr factors were excluded as immunizing antigens. In each case a high anti-A or anti-B titre was recorded in the mother.

John Murray

2035. **Iso-agglutinins in Cord Blood**
R. JAKOBOWICZ and L. M. BRYCE. *Medical Journal of Australia* [*Med. J. Aust.*] **1**, 669–673, May 29, 1948. 15 refs.

Cord blood from 355 babies was examined for anti-A and anti-B agglutinins. The authors state that anti-A and anti-B agglutinins do not filter through the placenta like bacterial immune bodies or Rh antibodies. They cite, among others, a case in which the maternal antibody titre was 2,000 but no agglutinins could be demonstrated in the cord blood. A and B agglutinins appear oftener in the cord blood when the mother is of group O than

if she is of group A or B, and generally the agglutinins in the foetus are very weak, or may be completely absent. However, in four cases agglutinins incompatible with the baby's cells were found in the cord blood. It is suggested that these were immune bodies whose formation was stimulated by the foetus in each case, and that the immune bodies are smaller, and can therefore cross the placenta easier than natural α and β agglutinins. The authors believe that the mother provides the antibody found in cord blood in cases of homospecific pregnancy in which the antibody could have arisen in the mother or foetus. *John Murray*

INSECTICIDES AND REPELLENTS

2036. **Studies on the Use of DDT and Phenyl Cellosolve for Control of Pediculosis in Villages in Colombia**
J. A. MONTOYA and P. P. OSEJO. *American Journal of Hygiene* [*Amer. J. Hyg.*] **47**, 247–258, May, 1948. 2 figs., 11 refs.

Louse-borne typhus is endemic in certain small highland communities in Colombia, where the inhabitants live under ideal conditions for the propagation and spread of lice. The experiments described in this paper were undertaken, first to determine whether DDT dusted on the body and on fomites, and used in combination with " phenyl cellosolve " applied to the head, would provide an effective and inexpensive method of delousing the inhabitants of such isolated rural villages, and secondly to assess the minimum frequency of application of these substances necessary to maintain the louse infestation index at a level sufficiently low to render unlikely the transmission of louse-borne typhus on a significant scale.

" Two studies of 1-year duration of louse control among the inhabitants of two small primitive Colombian communities are described. In one, techniques and administrative methods were developed for mass delousing procedure using DDT-10 and 5 per cent phenyl cellosolve lotion with the objective of maintaining the louse-infestation rate at a level sufficiently low to render unlikely the transmission of louse-borne typhus. In the other, the objective was to determine the time interval for the louse infestation to reach its original level following one single application of the insecticides to as many of the inhabitants as could be reached."

Hand dusters were used exclusively for applying the DDT-10, while the 5% phenyl cellosolve was rubbed on the scalp in the form of a shampoo. Two weeks before the application of the insecticides, a complete census was made of the population and buildings, sketch maps of the towns were prepared, and the buildings were all numbered, while a propaganda campaign, sponsored by the ecclesiastical and civil authorities, was instituted. In addition to these verbal appeals " small bars of soap and combs, as well as some linens and clothing, were also distributed to the poorest inhabitants in order to assist further in arousing public collaboration ". In spite of these careful preparations, a proportion of the inhabitants evaded part, or all, of the treatment, the exact proportion of missed cases at each treatment being shown in a table. These missed cases, together with immigrants from other villages, formed a focus of reinfestation for the treated population; thus, in the village whose inhabitants received a single application of insecticide, although the body-louse and head-louse infestation rate dropped from 76·8% to less than 5% following treatment, it rose to 60% at the end of a 10-month observation period. If, however, the treatment with DDT and cellosolve was repeated every 4 months, satisfactory results were recorded, as is shown by the following statement quoted from the authors' conclusions: " The results in Imues and Yacuanquer indicate that it is practicable and relatively inexpensive by periodic use of DDT and phenyl cellosolve to maintain the louse-infestation index of an entire community at a level sufficiently low to preclude typhus outbreaks and to reduce the incidence of the disease to a position of minor public health importance. They indicate that careful applications of these insecticides at intervals of 4 months to at least 98% of the population should maintain the louse-infestation rate at or below 5% ". *R. M. Gordon*

2037. **Toxicity of Hexachloro*cyclo*hexane.** (Recherches sur la toxicité de l'hexachloro*cyclo*hexane)
M. J. DALLEMAGNE and E. PHILIPPOT. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **76**, 274–296, May 1, 1948. 15 figs., 47 refs.

The γ-isomer of hexachloro*cyclo*hexane is widely used as an insecticide (" gammexane "). Continued administration of this substance to 6 dogs by various routes and in daily doses of 20 mg. per kg. intramuscularly to 100 mg. per kg. by stomach tube produced toxic effects—convulsions or anorexia, both terminating in death. There were no changes in blood levels of calcium and potassium in the animals. Two rabbits appeared less sensitive to repeated injections of gammexane. They died of pulmonary oedema. The drug accumulated particularly in lipid-rich tissues and there was evidence of liver damage in some animals. Typical convulsions occurred in dogs after a single dose of 100 mg. per kg. orally in oil, after a delay which was greater if the animal rested quietly. Intravenous injection of 1 mg. of gammexane per kg. in alcohol caused mixed clonic and tonic convulsions almost at once. Larger doses of aqueous solution are necessary. The convulsions did not occur in the " spinal " dog, and were abolished or prevented by barbiturates, curare, " myanesin ", and the curarizing substance " 3,381 R.P.".

The rise in blood potassium concentration noted during the convulsions is believed to be a secondary effect. It did not occur if the convulsions were prevented by curare and it fell to normal when convulsions were controlled by a barbiturate. Blood calcium levels showed little change. The convulsions are largely of central origin. Reports of toxic effects due to gammexane may be less frequent than those of DDT toxicity because gammexane is a slightly soluble powder and has an unpleasant smell. In oily solution it is more dangerous, being better absorbed, and no obvious warning signs of overdose may be seen. *Derek R. Wood*

Jurisprudence

2038. **Treatment of Criminal Psychopaths in the Detention Institution and Mental Hospital at Nykobing, Seeland, Denmark.** [In English.]
O. JACOBSEN. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] Suppl. 47, 42–53, 1947. 1 fig.

The Detention Institution is a separate house within the hospital but is run in connexion with the latter under the same management and partly with the same staff, including the medical staff. It is used for intractable insane males and combines the security of a prison with the advantages of hospital facilities for care and treatment. Fifty patients are accommodated, with a staff of 36 males. No mental defectives are now admitted and psychopaths are only admitted when their behaviour is such that they cannot be retained in the mental hospital; of 47 patients 18 are classified as schizophrenics, 18 as psychopaths, 9 as epileptics, and 2 as paranoids. The crimes committed include manslaughter and other crimes of violence.

The advantage of the detention block is that such patients may be a great nuisance to other patients in the hospital, while many of them are not in the ordinary sense of the term psychotic. It is very necessary to afford them, especially the younger group, occupation and training for re-entry into society. The training should be similar to that given in evening schools. It would be advantageous to transfer them to private homes before their discharge and to ensure effective follow-up until they settle down in life. If such patients are kept in a mental hospital public prejudice against sending relatives to the hospital is increased, but the hospitals are responsible for the treatment of the mentally ill and it is difficult to lay down strict rules. In view of this and the fact that psychopaths and epileptics so often are a disturbing influence in a ward, a separate detention block is desirable for those who cannot be submitted to the ordinary regime of the hospital and to a treatment that corresponds completely with that of other patients. If they can conform to the ordinary hospital conditions, then those sent by courts and other legal agencies may well be treated in hospital with the full advantages of occupation, training, and whatever aftercare is available, though they cannot of course be discharged without a court order.

R. G. Gordon

2039. **Medical Aspects of Juvenile Delinquency**
W. F. SCHNEIDER. *Ohio State Medical Journal* [*Ohio St. med. J.*] **44**, 260–264, March, 1948. 6 refs.

The author urges comprehensive study of the reasons for the behaviour of any particular delinquent, and that the possible effects of somatic disturbances should not be overlooked. For example, truancy in a patient with Fröhlich's syndrome may be due to the teasing of other children, and hyperkinesia to the tensions induced by the overdriving both in home and school of the chronically fatigued child. The allergic child may be driven " crazy " by the constant restrictions of an anxious mother. In 53% of a series of 500 cases there were abnormal physical findings; only 3% were free from physical defect of some sort in a group reviewed by Wallace. The author recalls the effects of encephalitis on behaviour, and the association of epilepsy and cerebral dysrhythmia with delinquency, though he properly warns against too much stress on so-called abnormalities when the range of normality of cerebral rhythms is still not firmly established. Psychomotor behaviour may well be a manifestation of loss or absence of cortical control and the lack of response to treatment in patients with psychopathic personality may be organically or constitutionally determined. Physical dysfunctions, such as visual or auditory defects, may similarly be closely related to asocial behaviour and " physicians may be concerned with the physical aspects of disease and defect to the exclusion of adequate consideration of the influence of that disease or physical defect on personality and behaviour ".

R. G. Gordon

2040. **Delinquent Defectives—A Group Study**
J. V. MORRIS. *American Journal of Mental Deficiency* [*Amer. J. ment. Defic.*] **52**, 345–369, April, 1948. 29 refs.

Recently it has been suggested that there has been an increase in the numbers of delinquent defectives in the colonies and certified institutions in England. To test this an investigation was made into the case histories, family histories, and environmental factors of all patients on the books of the Norfolk County Council Institutions, including those patients on licence. It was found that in general, environmental factors were more important than was the mentality of the offender. This is borne out by the literature quoted. Epileptic and post-encephalitic patients were excluded from the enquiry. In 80% a contributory cause to the delinquency was found—defective family relations, defective discipline, or a vicious home. Sexual offences predominated, constituting 42·8% even when girls described as being in moral danger were excluded. Larceny comprised 26·7%; arson, which is supposed to be associated with mental deficiency, was uncommon. A conscious or semi-conscious feeling of inferiority was common and probably contributed to the delinquency. Defectives cannot find, or fear to approach, a sexual partner of their own age, so tend to turn to juveniles or perversions to obtain satisfaction. Larceny is practised to enhance the personality and the stolen goods are often given away to curry favour. A further factor in establishing inferiority is the inability to get and keep a job.

Treatment must consist of " resocialization " by the building of character, sound habit training, and the

teaching of a trade which can be learnt. By such means, many can be brought to a state in which they are able to leave the institution, but they need supervision and help. There is a hard core of 20% of permanent institutional patients who resist resocialization because of their non-cooperative social attitude.

Three illustrative cases are quoted in detail.

R. G. Gordon

2041. **Delinquency and Epilepsy: A Clinical and Electrophysiological Note**
R. S. HODGE. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 439–443, April, 1948. 4 figs.

A study is made of the help given by electroencephalography to psychiatric expert witnesses in assessing the state of an accused person's mind " at the time of committing the offence " and in deciding whether he knew what he was doing. Of delinquents studied three groups were differentiated as epileptic: (1) those with fits; (2) those without fits but with various epileptiform manifestations during hyperpnoea; (3) those in whom the only epileptic phenomena were electroencephalographic. These observations show that the incidence of epilepsy amongst delinquents is high. If it can be shown that an accused is subject to episodic disturbances in which cortical integration is affected it is reasonable to infer, in the author's opinion, that at some material time he did not know what he was doing and possibly that he did not know the difference between right and wrong. This is specially the case in juveniles in whom the process of cerebral maturation is incomplete. This reinforces Henderson's plea for an indeterminate sentence in the case of juvenile delinquents, discharge to be dependent not upon the expiration of time but on the proper establishment of social patterns.

R. G. Gordon

2042. **Criminal Behavior of Mentally Retarded Adults**
A. E. GRIGG. *American Journal of Mental Deficiency* [*Amer. J. ment. Defic.*] **52**, 370–374, April, 1948. 4 refs.

This study was carried out at the Virginia State Penitentiary to investigate the factor of mental deficiency in criminal behaviour. Army records do not suggest that the intelligence of criminals differs significantly from that of the normal draft. Twenty-five definitely low-grade criminals were studied. The crimes fell into three groups: (A) crimes, chiefly of violence, committed as a result of momentary impulse; (B) crimes of stupidity or suggestibility consonant with the mental deficiency; (C) crimes undertaken for personal advantage, such as increasing income. In all cases there was an obvious lack of foresight in assessing the probable effects of the crime. Such criminals are more than usually prone to excessive use of alcohol. They appear to be impulsive not because of their emotional make-up but because it is their nature to react to the present with little ability to project their acts either to the past or to the future. Such persons should not be sent to prison but to institutions; their condition should have been detected before their arrest. On the average mental defectives do not tend to be criminal, and even those who are may be helped by an appropriate programme of education and resocialization.

R. G. Gordon

2043. **An Investigation on the Significance of Cerebral Injury in the Development of Criminality.** (Eine Untersuchung über die Bedeutung der Hirnschädigungen für die Entstehung der Kriminalität)
M. KAILA. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] Suppl. 47, 80–91, 1947. 6 refs.

Two groups with cerebral injury were investigated. Group I consisted of 573 adult males injured between 1929 and 1934, and living in 1942 when the information was obtained from insurance records. As a control for each case another injured person was taken of similar age, sex, occupation, living place, and social status, and whose injury, though not cerebral, was of similar severity and had produced a comparable degree of disability. Group II contained 203 males injured when under the age of 20 between 1920 and 1929, cases being collected from hospital records. Controls were too difficult to obtain. Information regarding criminal offences was obtained from the penal register in 1942 and 1946 respectively. Injuries included simple concussion, simple skull fractures and fractures of base of skull, injuries with localizing symptoms, cerebral contusion, and severe fractures with concussion. The percentages of the different types of offences in group I and in controls were similar; analysis into offences committed before, after, or both before and after the injury revealed no real difference between group I and controls. From the Finnish criminal statistics it was possible to estimate the probable number of sentences of imprisonment for a group of known ages over a defined period. After division into types of offences, this estimated mean criminality and the ratios: actual sentences of imprisonment/mean criminality were compared in group I and in controls both before and after the injury. The figures for group I and controls correspond with the estimated mean criminality, as regards both general criminality and its subgroups. The general criminality for group II corresponds to the mean, but for reasons given the figures for offences against property are apparently higher. Figures from another of the author's investigations are given, showing that the criminality of brothers of persons once sentenced for an offence against property was 2½ times as high as the mean criminality, that of brothers of repeated offenders and those committing crimes of violence higher still. It is concluded that cerebral injury has no general significance as a cause of criminality. The cases in which post-traumatic character change causes criminal acts are exceptions. Close relationship with a criminal is of much more significance than is cerebral injury, even when the latter has occurred in childhood. *W. Forster*

2044. **Examination of Genitalia in Attempted Rape.** (O exame genital nos casos de atentado ao pudor)
F. COIMBRA. *Portugal Médico* [*Portugal méd.*] **32**, 105–117, March, 1948.

See also Section Psychiatry, Abstract 2251.

Radiology

2045. **The Effect of Radiation on Hemopoiesis. Is there an Indirect Effect?**
J. S. LAWRENCE, W. N. VALENTINE, and A. H. DOWDY. *Blood* [*Blood*] **3**, 593–611, May, 1948. 3 figs., 58 refs.

The authors attempt to answer the question whether *x*-irradiation results in the formation of specific substances (not merely those liberated by non-specific cellular injury), which when transported to distant areas produce a characteristic indirect effect. The literature is reviewed and found to be contradictory. In the experiments 26 cross-circulation anastomoses (carotid to carotid) were made between normal and irradiated cats. The criteria used were leucocyte and lymphocyte counts. Cross-circulation was established mostly after the irradiation of one partner, at all intervals up to 82 hours; in 7 cases, anastomosis was established and irradiation of one partner carried out while the other was shielded. Technical factors included a dose of 1,500 r to the whole body at 250 kV, with a 22-in. (55 cm.) distance from the target to the middle of the cat and a half-value layer of 2·1 mm. Cu, 25 r per minute being delivered. Details of the leucocyte and lymphocyte counts during 28 days of follow-up are given.

In some cases in which one partner had received irradiation at the time of or shortly before anastomosis, a striking degree of leucocytosis was found, the cause of which is obscure. A trend towards slightly lowered lymphocyte counts in the non-irradiated animals is not considered significant. In no instance did leucopenia develop in the normal animal. It is concluded that no significant indirect effect of radiation was demonstrated. The authors accept the findings of other workers that structures at a distance from the site of irradiation (especially lymph nodes) may be affected, but consider that this may be adequately explained as a non-specific effect, such as takes place after other forms of injury also.

J. Walter

2046. **Some Hematologic Effects of Irradiation**
W. BLOOM and L. O. JACOBSON. *Blood* [*Blood*] **3**, 586–592, May, 1948. 26 refs.

Since some radiologists still hold that small doses of radiation stimulate cellular activity, the authors made a special study of the blood-forming organs and peripheral blood in a considerable experimental series. The bodies of rabbits, rats, mice, and guinea-pigs were irradiated by *x* rays and γ rays, fast and slow neutrons, starting usually with the LD 50/30 days dose of each and decreasing until no histological or haematological changes were found. In most cases the dose was given in one exposure. Equivalent doses of all types of radiation used produced similar effects.

The earliest observable changes in the blood-forming organs, usually within the first hour, were degenerative changes and death of cells; there was no evidence of increase in mitosis. In 1 week to 2 weeks haematopoiesis was resumed, but rarely reached or exceeded normal limits in the bone marrow. With progressively smaller doses, the effects became minimal at 50 r and just detectable at 25 r; with still lower doses no changes were found. The only instance of subsequent overcompensation was in bone marrow of surviving rabbits, which seemed hyperplastic within 2 months of exposure. In the peripheral blood, an increase in circulating heterophil leucocytes occurred within the first 24 hours, followed by leucopenia; lymphocyte, monocyte, eosinophil, reticulocyte, and platelet counts were always reduced. As recovery occurred, a compensatory increase above normal was not uncommonly found, especially for heterophils and reticulocytes but not for lymphocytes. After chronic irradiation (small doses being given daily for up to 4 years) any effect on the peripheral blood was always a reduction in number of circulating cells.

Results of focal irradiation were also studied. In mice exposed to large amounts of β rays from plaques containing P^{32} placed on the skin overlying the spleen, the zone of radiation damage in the part of the spleen adjacent to the skin gradually merged into normal spleen at a greater depth. No evidence of a zone of hyperplasia was found, although this would be expected near the periphery of the range of penetration of the β rays if a stimulating effect does occur. In most of the experiments intravenous or intraperitoneal injections of radioactive isotopes (Ra, Pu, P^{32}, Sr^{89}, Y^{91}, Zr^{40}, Ba^{140}, La^{140}, Na^{24}) were given. Most of these accumulated in bone or the red pulp of the spleen, resulting in hypoplasia of bone marrow; secondary ectopic myelopoiesis in the spleen usually followed. Primary stimulation of blood-forming tissue, reflected in the peripheral blood, was never found; compensatory increases were occasionally found.

The literature is discussed and it is concluded that there is no evidence of primary stimulation of haematopoiesis; compensatory increases can occur, but are always preceded by a reduction. The initial leucocytosis seen after acute exposure is probably a reaction to injury by mobilization of cells rather than by new formation of cells.

J. Walter

2047. **Radioautograph Technique with C^{14}**
A. M. MACDONALD, J. COBB, and A. K. SOLOMON. *Science* [*Science*] **107**, 550–552, May 21, 1948. 3 figs., 4 refs.

A new technique is described for the production of radioautographs [autoradiographs] from tissue sections. For the accurate location of radioactive material an autoradiograph must be permanently and accurately superimposed on the stained section and, in addition, it is desirable that normal staining procedures should be

applicable, that there should be intimate contact between the section and the photographic emulsion, and that the resulting slide should be suitable for microscopical examination at high magnifications. The sequence of development and staining should be immaterial, and when section and film are not separated the developer and stain must each affect only the relevant part of the combined preparation. The simple method of contact photography from the prepared section has the disadvantage of yielding a double picture, with the difficulty of exact superposition especially at high magnifications, and no technique hitherto developed satisfies all the above criteria. In the present method, stripping film (10 μ emulsion, 7 μ base) is cemented on to the section, from which the emulsion is separated by the film base; after development the layers are inverted on to another slide to expose the tissue section for staining, the base in each case protecting the layer not concerned in the treatment. Paraffin is removed with xylol, the slide washed in absolute alcohol, dried, and covered with 1% celloidin. The film is applied and pressed with fine, hard filter paper until dry; celloidin must not run on to the emulsion. The specimen is covered with the guard slide and exposed under 12·5 lb. per sq. in. (0·88 kg. per sq. cm.) pressure. The film is processed in a test-tube with distilled water; all precautions for fine development must be observed. After processing, the film is inverted and attached to another slide with " kodalith " stripping cement and when dry may then be treated as a normal section.

The technique was developed to study the uptake of C^{14} in rabbit liver. Sections 2, 5, and 10 μ thick of liver from rabbits starved for 48 hours are incubated *in vitro* with $NaHC^{14}O_3$ in the presence of pyruvate substrate for 2 hours and fixed in Rossman's fluid. The figures show a section of rabbit liver pre-stained with haematoxylin and eosin at magnifications of $\times 110$ and $\times 600$, and a section pre-stained by the Feulgen Bauer method for glycogen at $\times 400$; colours are not shown. In some sections (not shown) the celloidin appears to have produced dense fogging. Further investigations on this subject and full details of technique and the emulsions tested are to be published. *R. S. Quick*

2048. **Effective Compression in Excretory Pyelography**
H. R. ZATZKIN. *Radiology* [*Radiology*] **50**, 639–644, May, 1948. 7 figs., 11 refs.

Compression in excretory pyelography is obtained by placing a sphygmomanometer cuff between the anterior superior iliac spines, approximately 1 in. (2·5 cm.) above the pubis, beneath a binder which is tightened as much as possible. A preliminary radiograph is taken without compression and then " neo-iopax " is introduced slowly, 30 ml. being given intravenously in 1 minute. At the expiration of 5 minutes a second film is exposed and the rubber tube from the cuff is attached to the recording apparatus. A pressure equal to 110 mm. Hg will completely occlude the ureters in the majority of instances. In a stout person, or one of heavy musculature, 120 mm. Hg pressure may be necessary. Pressure beyond 120 mm. Hg is poorly tolerated and for thin subjects 100 mm. Hg will usually suffice. Fifteen minutes after the injection a third film is exposed with the pressure apparatus in place. The patient is then placed in the upright position and the fourth exposure is begun no later than 10 seconds after the release of pressure. This usually results in good visualization of the lower ureters. Speed is essential in making this exposure. In cases of hypertension when the radio-opaque material is excreted quickly, the first film is exposed after 3 minutes and pressure then applied, an additional film being taken after a further 9 minutes.

The author claims that, even if the pressure is insufficient to occlude the ureters completely, the pelvis and calices are well seen and, in the majority of cases, the density of shadow in the excretory pyelogram approaches that obtained by the retrograde method. The short duration of the compression is, in his opinion, not sufficient to give rise to dilatation beyond the limits of normal physiological distensibility, as is also the case in retrograde pyelography, and thus difficulties of interpretation from over-dilatation do not arise. Abdominal compression by this method eliminates the need for many retrograde examinations, as a better view of the renal sinuses is obtained. *L. G. Blair*

2049. **The Association of Colchicine with *X* rays in the Treatment of Malignant Tumours.** (A propos de l'association colchicine-roentgenthérapie dans le traitement des tumeurs malignes)
J. M. REVIGLIO. *Radiologia Clinica* [*Radiol. clin., Basel*] **17**, 149–155, May, 1948.

The use by French workers of this combined treatment is discussed. Colchicine is given intravenously in increasing doses starting with 2 mg. every 2 days or twice a week. Four hours after the injection radiotherapy is started, the dose being not more than 250 r daily. Five cases of advanced malignant disease were given between 3,000 and 6,000 r in association with colchicine, and in all cases there was regression of the disease. The author considers that the two forms of therapy act in a purely additive manner, but that the colchicine may reach tumour cells unaffected by radiation.
J. Maclean Smith

2050. **Physical Basis for the High Skin Tolerance of Supervoltage Roentgen Rays**
J. G. TRUMP. *Radiology* [*Radiology*] **50**, 649–656, May, 1948. 2 figs., 12 refs.

The tendency for skin tolerance to *x* rays to increase with increasing kilovoltage has been recognized in the lower voltage ranges for a considerable time. This has now been confirmed by observations on skin erythema doses up to 3,000,000 volts. In the latter range three or four times greater doses can be given to deep lesions than are possible at 200 kV, with the same skin reaction. The commonly accepted explanation for the higher erythema dose of high energy radiation is that the ionization is not maximum at the surface. The ionization rises to a maximum at a depth depending on the mean range of the secondary electrons produced by the

x rays. For example, with 4,000,000-volt radiation, the surface ionization is only 25% of the maximum, which is reached some 4 mm. below the surface. The author points out that this electronic equilibrium effect only accounts for some 80% of the variation of erythema dose with *x*-ray quality. It is suggested that the variation is accentuated by the lower specific ionization along the initial part of tracks of secondary electrons produced at the very high voltages. This further reduces the biological effectiveness of radiation energy absorbed in the superficial layers. *J. E. Roberts*

2051. **Radiation Injuries of the Intestines**
C. W. HOCK, J. RODRIGUES, A. HAMANN, and W. L. PALMER. *American Journal of Medicine* [*Amer. J. Med.*] **4**, 511–524, April, 1948. 9 figs., 17 refs.

The authors review the course, symptomatology, pathology, and prognosis in cases of intestinal damage after irradiation of cancer of the female genitalia, and analyse in detail 19 severe reactions occurring in a series of 344 patients treated for cancer. Of 170 patients with cancer of the cervix, 9·4% developed severe bowel reactions, as did 2·9% of 101 with corporeal growths. Treatment of carcinoma of the ovary, vagina, and vulva was not followed by intestinal injury. Six of the 19 patients died, death at least being accelerated by the radiation effects. One other committed suicide.

Some degree of reaction occurs in one-half to two-thirds of the cases treated by combined radium and *x*-ray therapy, the necessary lethal dose for the cancer being sufficient to produce at least a mild reaction. It is doubtful whether a dose adequate for cancer can be given without sometimes producing severe bowel effects, but a high intensity of irradiation, overlapping of areas intensely irradiated by radium and *x* rays, faulty placing of radium, falling of the uterine radium into the vagina, retroversion of the uterus, and adhesions from old pelvic sepsis contribute to the frank overdosage, which is the most important causal factor. Symptoms of early reaction are a burning sensation in the pelvis, frequency of micturition and defaecation, and diarrhoea, clearing up in about 2 weeks. In late cases there may be symptoms of incomplete intestinal obstruction and rectal haemorrhage, diarrhoea, tenesmus, and severe pain, with marked deterioration in the general condition. In the earlier and more acute phase there is diffuse hyperaemia of the rectal wall, which bleeds readily on touch, with occasional ulceration. In the late reactions fibrous stricture, necrotic ulceration, telangiectasis and atrophy, and perirectal fibrosis are observed. Fistulae may form. Differential diagnosis between malignancy and radiation injury may only finally be made by improvement in general health after treatment or after resection of the damaged tissues. Biopsy is hazardous on account of the risk of frank necrosis and fistula formation.

The best treatment is prophylaxis by careful planning and execution of irradiation treatment. Rest in bed, rectal lavage or instillation of bland oil, maintenance of general health, colostomy for obstruction, and resection of damaged tissue may be called for when the condition is established.

[Todd classified pelvic irradiation reactions according to their site, calling the purely rectal ones " intrinsic ", and perirectal and general pelvic fibrosis " extrinsic ". The former he thought to be due to direct local overdosage from either the uterine or vaginal radium, the latter to post-irradiation interference with the blood supply higher in the pelvis. Dose levels advisable for the treatment of cervical cancer at 50 years of age may cause quite severe " intrinsic " (and occasionally " extrinsic ") reactions at 70 years. The high incidence of rectal reaction after combined *x*-ray and γ-ray irradiation emphasizes the danger of independent administration of the two forms of therapy without planning of the whole treatment. Operative procedures within the actual field of reaction often fail owing to the inability of the sclerosed tissues to heal, but fibrous rings soften and fistulae are said to close spontaneously after some months, particularly if local irritation is removed by colostomy. The differential diagnosis of radiation reaction is important, for such rectal lesions have been irradiated as rectal cancers, and perirectal fibrosis has been subjected to " palliative " *x*-ray therapy because of a mistaken diagnosis of advancing neoplasm, with unfortunate results for the patient.] *John R. Nuttall*

2052. **Effect of Low Dosage Roentgen Radiation on the Gonadotropic Function of the Hypophysis of the Mature and Immature Female Albino Rat**
J. H. FREED, E. J. FARRIS, D. P. MURPHY, and E. P. PENDERGRASS. *Journal of Clinical Endocrinology* [*J. clin. Endocrinol.*] **8**, 461–481, June, 1948. 1 fig., 53 refs.

Although low-dose *x*-ray treatment of the pituitary and ovaries has long been used in treatment of menstrual disorders and sterility, the mode of action of the therapy was ambiguous and it was not known whether the action was due to direct stimulation of glandular function through alteration of biochemical factors, or to the secondary effect of increased blood supply, or to the selective destructive action of *x* rays. It was therefore decided to carry out experiments involving the irradiation of the hypophyses of albino rats with low doses of *x* rays, and to note any alteration in glandular function and the mechanism by which such changes were effected. Previous experiments suggested that the gland was radioresistant, being histologically unaffected by doses up to 400 r.

Two main experiments were involved; in one the authors used sexually mature female Wistar albino rats; and in the other sexually immature rats of the same breed. The oestrus cycle of these rats lasts for 4 to 5 days, the first day being that of most activity, the day of heat. With the sexually mature females, doses from 5 r to 300 r were directed to the pituitary from an intermediate therapy unit of output 90 (air) r per minute at skin surface. After single and serial doses delivered on the second day of the cycle, 49·1% of the rats showed symptoms of recurring heat—increased activity and copulation response. Anatomical studies revealed an increased vascularity in some rats, and a significant increase in weight of the pituitary over that of the 2-day control rats. The ovaries and uteri showed little difference in weight. In

rats irradiated on the third day of the cycle there was no recurrence of heat symptoms. The sexually immature females were irradiated with doses of 5 to 50 r in single and in split doses. No difference was observed between them and their controls, either in the appearance and weight of glands and uteri, or in the age of vaginal opening.

That *x* rays have an effect on the pituitary is indicated by the reappearance of heat in 49·1% of one of these groups and in the increased weight and vascularity of the gland in this group. But it is a transient effect; the periodicity of the cycles is unchanged, and subsequent cycles are normal. That this transient effect is not due to a direct stimulating effect of *x*-rays is also shown by the inability to produce sexual precocity in young rats, even though small doses of follicle-stimulating hormone produce this precocity. Work on other organisms supports this view. The non-recurrence of heat in 50·9% of the 2-day irradiation group is thought to be due to well-established metoestrus, so that there is insufficient follicle-stimulating hormone to overcome the progestin dominant at metoestrus. The transient acceleration of metabolism observed is therefore regarded as secondary to increased vascularity or altered cell permeability produced by irritative effects of small doses of *x* rays, not visible histologically. That *x* rays do not directly stimulate normal cell growth is shown by these experiments. *Ralston Paterson*

2053. **Hydronephrosis: A Radiologic Classification Based on Anatomical Variations**

S. A. ROBINS and J. FISCHMANN. *Radiology* [*Radiology*] **50**, 632–638, May, 1948. 14 figs., 19 refs.

For the purpose of this study 682 unselected radiographs of 1,217 kidneys were analysed. A total of 61 (9%) in which hydronephrosis was shown were excluded for the purpose of normal measurement, but are used for the classification of the types of hydronephrosis. The average measurements of normal kidneys were found to be as follows, the width of the parenchyma being measured from the tip of the middle calix to the nearest point of the outer border of the kidney. The length in males was 12·6 cm. and in females 12·3 cm.; the width in males was 5·65 cm. and in females 5·77 cm.; the width of the parenchyma in males was 2·2 cm. and in females 2·35 cm.

Anatomically and radiologically there are 3 types of pelves as regards relation to the kidney parenchyma, namely, intrarenal, intermediary, and extrarenal. The figures for incidence of the different types of pelvis in males and females are: intrarenal 43·1 and 18·4%; intermediary 56·3 and 77·3%; extrarenal 0·6 and 4·3%. It is further shown that the relative frequency of the intrarenal and intermediary types of pelvis varies with age, the pelvis intruding into the kidney substance with advancing years.

The authors have classified hydronephrosis into intrarenal, combined, and extrarenal in a manner analogous to that used in classifying the type of pelvis. Thus, intrarenal hydronephrosis designates dilatation restricted to the intrarenal portion of the drainage system of the kidney. It may involve all or any one of the calices, with or without dilatation of the pelvis. This is the type of hydronephrosis that occurs most frequently in intrarenal pelves. Combined hydronephrosis involves simultaneously both the calices and the pelvis, occurring most frequently in intermediary pelves. Such cases constitute the majority of all cases of hydronephrosis; this is to be expected in view of the fact that most pelves are intermediary. In extrarenal hydronephrosis the dilatation is restricted to the renal pelvis. It may occur in the extrarenal as well as the intermediary type of pelvis.

Hydronephrosis is a potential source of danger to the excreting tissue of the kidney. The most severe damage to the parenchyma results from the intrarenal type, the combined type producing less, whilst it is virtually non-existent with the extrarenal type. The width of the parenchyma as measured by excretion urography is an index of the degree of damage to the parenchyma. The authors believe that any width less than 1·45 cm. is pathological. *L. G. Blair*

2054. **Importance of Intra-alveolar Pressure in the Diagnosis of Pulmonary Diseases**

N. WESTERMARK. *Radiology* [*Radiology*] **50**, 610–618, May, 1948. 7 figs.

The filling of the pulmonary vessels depends to a great extent on the intra-alveolar air pressure, the vessels being compressed when the pressure is high and dilated when it is low. To obtain such changes of pressure, one shank of a manometer is connected by means of a rubber tube and mouthpiece to the patient's mouth. The patient is told to take a shallow inspiration and then to suck through the mouthpiece until the level of the liquid registers a pressure of −5 to −10 cm. of water. The radiograph then taken is used as the standard. To obtain films at low pressure, the patient is first requested to take a light inspiration, and then to augment the inspiratory movement with closed mouth and nose until the pressure falls to −40 cm. To obtain films at high pressure, the patient is again asked to take a light inspiration. He must then, by blowing with closed mouth, press the water level of the manometer up to a positive pressure of 40 cm. of water.

The author first claims that, by determination of the point at which the arteries at the hilum are diminished in size, a rough estimate of the pressure in the pulmonary arteries can be obtained, and that this serves as a guide to the degree and prognosis of mitral lesions. Further, because the vascular structures at the root are compressible, it is easier in the high-pressure film to demonstrate glandular enlargement at the hilum. In moderate degrees of congestion and in pulmonary oedema, radiographs made under high-pressure conditions will show a marked diminution or disappearance of the shadows. In acute bronchopneumonia and acute lobar pneumonia the opacities frequently become more distinct in outline. In acute and chronic atelectasis, in chronic pneumonia, and in most cases of tuberculosis of the reinfection type, changes are minor or absent altogether when the pressure is altered. *L. G. Blair*

Pathology

2055. **Role Played by the Salivary Glands in the " Alarm Reaction "**
W. E. EHRICH and J. SEIFTER. *Archives of Pathology* [*Arch. Path.*] **45**, 239–245, Feb., 1948. 12 figs., 11 refs.

Parenchymatous changes in various organs, namely, thymus, spleen, lymph nodes, and gastro-intestinal tract, present in shock in experimental animals are also found in poisoning with substances such as colchicine, amidopyrine, and selenium compounds. The loss of secretory granules in the cells of the pancreas was of interest to the authors and an attempt was made to discover whether similar changes occurred in the salivary glands. Three series of 7 to 8-week-old rats were given 5, 7 and 10 mg. of colchicine per kilo body weight by subcutaneous injection; 10 out of 21 rats died 18 to 24 hours later and the others were killed 2 to 28 hours after injection. The expected changes of the " alarm reaction " were found and in addition marked loss of zymogen granules had occurred in the salivary glands; in the more severe cases there were foci of necrosis. Similar changes were found in rats, rabbits, and dogs given the other poisons listed. A possible aetiological factor leading to involvement of these particular organs is thought to be their high nucleic acid content, particularly of ribose nucleic acid. The authors discuss the possible bearing of these findings upon the cause of the type of parotitis which afflicts the severely-ill patient. *W. S. Killpack*

2056. **Malignant Disease in Nigeria: An Analysis of a Thousand Tumours**
B. G. T. ELMES and R. B. T. BALDWIN. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **41**, 321–328, Dec., 1947. 4 figs., 13 refs.

In this paper an analysis is made of 1,000 specimens of tumours received from all parts of Nigeria during the 10 years 1935–44. All the tumours were from Africans. The tumours are classified according to variety of tumour, age and sex incidence, and type and site incidence, and the results are presented in tables [which should be consulted in the original]. Comment is made on several types of particular interest.

The series contained 45 examples of neuroblastoma of which 23 specimens were retinoblastomata; only 1 of the patients of known age was over 20. Sixty-three cases of melanoma were observed, despite the reputed rarity of melanoma in negroes. The site incidence supported the view that trauma was a significant aetiological factor; 45 (72%) of the tumours were on the foot and 4 had metastasized to the inguinal lymph nodes. The tumours were, for the most part, of spindle-cell or polyhedral-cell type, pigment usually being abundant. Melanoma is possibly less " aggressive " in Africans than in light-skinned races but accurate statistics are not available. There were 81 primary tumours of the liver; in all these livers there was cirrhosis of Laënnec type. The authors consider that the explanation of the frequency of primary liver tumours in tropical races will follow from an explanation of the high incidence of liver damage and consequent cirrhosis and that dietetic factors are the most likely initiators of liver damage. Attention is drawn to a lesion with distinctive clinical appearances, described as " squamous carcinoma of chronic leg ulcer type ". Twelve examples were studied. The initial lesion was possibly a true tropical ulcer, although no evidence of fuso-spirochaetal infection was found. Out of 18 carcinomata of the bladder, 4 were associated with *Schistosoma haematobium* infection. Kaposi sarcoma was by no means rare in Nigerians, 24 cases being encountered; all were in males, and in all but 2 cases the lesions were restricted to the leg below the knee. The authors found no indication that the lesion was a granuloma of peculiar type. The histological picture was always predominantly neoplastic and the earliest nodule examined, probably not more than 6 weeks old, had the structure of an angiosarcoma.

Although an analysis of biopsy and necropsy material cannot give an accurate picture of the incidence of malignant tumours in Nigeria, the authors feel that it provides information of considerable value at this stage of the country's development. *L. Foulds*

EXPERIMENTAL PATHOLOGY

2057. **Comparative Susceptibility of the Lymphoid Tissues of Strain C57 Black Mice to the Induction of Lymphoid Tumors by Irradiation**
H. S. KAPLAN. *Journal of the National Cancer Institute* [*J. nat. Cancer Inst.*] **8**, 191–197, Feb., 1948. 3 figs., 10 refs.

The experiments recorded here were planned to provide evidence on the origin of lymphatic leukaemias and lymphoid tumours, since it is not known whether they arise from a single focus or organ and then become disseminated through the blood stream, or whether they appear simultaneously from multiple foci in different parts of the body. Strain C57 black mice of both sexes and 1 month old were subjected to fractional whole-body irradiation on 12 consecutive days, the total dosage being 1,008 r. At intervals of 1 to 4½ months small groups were killed and the lymph nodes, spleen, and thymus gland were studied histologically; fragments of these tissues were also implanted in mice to test for tumour development.

Lymphoid tumours arose in 15 to 28 mice within 57 to 135 days after the beginning of irradiation. Most of the tumours were confined to the thymus gland, being unilateral in 4 instances and bilateral in the remaining 10. In 4 animals the tumours extended beyond the thymic capsule into the mediastinal soft tissues, and in 1 case

a single focus of tumour was found in the lung. There was no histological evidence of involvement of the spleen or remote lymph nodes. The only positive bio-assays were obtained from 3 thymic tissue fragments, 1 of which came from a mouse in which there was no histological evidence of a lymphoma. The failure to find any tumour outside the thorax leads the author to conclude that such lymphoid tumours originate in a single focus and that their dissemination is a secondary phenomenon. They differ from other neoplastic processes in their greater ability to disseminate and to invade the blood stream.

H. G. Crabtree

2058. **The Carcinogenic Activity of 2-Acetaminofluorene. Characteristics of the Lesions in Albino Rats**

A. J. Cox, R. H. Wilson, and F. DeEds. *Cancer Research* [*Cancer Res.*] **7**, 647–657, Oct., 1947. 14 figs., 13 refs.

The addition of 0·004 to 0·5% of 2-acetaminofluorene (AAF) to the diet of rats even for 25 days causes tumours to arise at different sites some months later. In one series of 84 rats (22 male and 62 female) fed with a diet containing AAF the tumour incidence was as shown below:

Organ	Number of Animals with Lesions		Total Incidence, %	Proportion Malignant, %
	Male	Female		
Liver	21	57	93	22
Bladder	16	51	80	21
Lung	8	24	38	16
Head	5	21	31	92
Breast	3*	23*	31	31
Kidney	3	17†	24	25
Uterus	—	13‡	21	8
Thyroid	2	9	13	0
Gastrointestinal tract	1	4	6	60

* Includes one subcutaneous fibroma.
† Includes one carcinoma of the upper ureter.
‡ Includes one sarcoma.

Photomicrographs are reproduced and a detailed description of the histology of the tumours is given. Aminofluorene has the same effect as the acetyl compound. "In each such organ it has been impossible to draw a sharp line of distinction between non-neoplastic hyperplasia and tumour formation. The hyperplasia never involved all parts of an organ or tissue uniformly, but appeared only in foci, which suggests that there was gradual development of some of these foci until large, well-defined nodules were formed, or until sufficient penetration of adjacent tissues had taken place to classify the process as malignant growth. In portions of lesions which showed such 'invasion', the cellular structure was sometimes indistinguishable from that of other lesions which were localized. No evidence was seen to suggest a sudden transformation of hyperplastic to neoplastic cells, or of benign to malignant cells."

"The livers in our animals did not show frequent cirrhosis such as that found after feeding *p*-dimethylaminoazobenzene to rats, and we have seen no other morphological changes that might suggest a predisposing condition. Similarly, in other organs which were the site of proliferative changes, there was no reason to suspect any specific predisposing factor. Inflammation was associated with some of the pulmonary lesions, but a number were entirely without evidence of inflammation. Also, a number of inflammatory lesions in the lungs and elsewhere were not accompanied by any unusual proliferative changes. The rarity of the development of tumours in any but epithelial cells following the administration of acetaminofluorene, and the repeated localization of lesions in the same organs, suggest a specificity of the carcinogenic effect, possibly related to the metabolism or excretion of the substance."

I. Hieger

2059. **Factors Determining the Action of Colchicine on Tumour Growth**

R. J. Ludford. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 75–86, March, 1948. 4 figs., 15 refs.

The typical "colchicine effect" observed in the treatment of soft, highly-cellular, and rapidly growing mouse tumours with colchicine, in amounts just below the lethal dose, is tumour regression followed by recurrence; complete inhibition of growth or "cure" is achieved exceptionally. The present paper describes an experimental investigation of the factors which modify the colchicine effect.

Host factors (age, genetic constitution, and cumulative toxic action) and tumour factors (rate of growth; histological structure, and acquirement of tolerance) governed the therapeutic result. The greatest degree of regression was obtained in young adult mice because these tolerated the largest doses of the drug. Genetic constitution determined the degree of tolerance, sensitivity to the general toxic action, and also the sensitivity of the tumour capillaries, but these factors did not run parallel. When similar tumours were transplanted into C57 and A mice, equal doses of colchicine caused more haemorrhage and more regression in the tumours in the A mice than in those of C57 strain, although A and C57 mice were equally sensitive to the general toxic action of the drug. Cumulative toxic action prevented the administration of repeated large doses of colchicine. In any one strain, the magnitude of the colchicinic effect was proportional, in general, to the rate of tumour growth; the action on slow-growing tumours was negligible. It seemed that blood capillaries were less easily disrupted in firm than in soft tumours; a transplanted squamous-celled carcinoma and a transplanted fibrosarcoma, both of relatively firm consistency, responded less than was expected from their rate of growth. Tumours acquired tolerance to the drug after several large doses and then responded less to further treatment. Mouse carcinoma 63 was implanted in 10 mice; colchicine administered under the most favourable conditions indicated by the previous experiments caused complete regression in 5 mice, in which no tumour was observed during 1 year or at necropsy at the end of that time.

The similarity of the actions of colchicine and of bacterial filtrates on tumours is emphasized, the primary cause of regression in each case being haemorrhage. The swelling of tumour cells arrested in mitosis by colchicine presumably increased the pressure exerted by the tumour parenchyma on the capillaries and this effect, and to a much greater extent the toxic action of colchicine on newly-formed capillaries, provide a reasonable, if not complete, explanation of the haemorrhage-inducing action of colchicine. In the author's experiments haemorrhage in the tumours was so extensive that direct toxic action of colchicine on the tumour cells was probably not a significant factor in causing regression. It is possible, however, that direct toxic action on the parenchyma may be more important in the regression of tumours of other types, especially lymphomata and lymphosarcomata, for when toxic substances are injected into animals thymocytes and lymphocytes are the first cells in which injury can be recognized. *L. Foulds*

2060. **Mast Cells in Experimental Rat Sarcomas**
H. HOLMGREN and G. WOHLFART. *Cancer Research* [*Cancer Res.*] 7, 686–691, Nov., 1947. 5 figs., 33 refs.

Experimental sarcomata were induced in a special strain of white rats bred in the Karolinska Institute at Stockholm. Out of a total of 47 rats which developed tumours, 27 arose after subcutaneous injections of 20-methylcholanthrene, 16 after implantation of pellets of the carcinogen under the skin, and 4 after inoculation of benzpyrene. The majority of the resulting sarcomata were of the polymorphocellular or fibroblastic types, the remaining few being rhabdomyosarcomata. Mast cells were found to be more numerous in the former types of tumours than in the latter. Mast cells, however, were present in all the induced sarcomata and were found to develop locally within the connective tissue of the tumours; this suggests that they may take part in the reaction system against the tumour cells. The authors found that mast cells were generally well preserved in the necrotic areas of the tumours, and contend from this that they possess a greater power of resistance than do the tumour cells. The possible origin of mast cells is also discussed in detail. *A. Haddow*

2061. **Antibody Response to Tumor Inoculation in Mice, with Special Reference to Partial Antibodies**
P. A. GORER. *Cancer Research* [*Cancer Res.*] 7, 634–641, Oct., 1947. 15 refs.

It was previously shown that strain A mice carry at least two antigenic factors (antigens I and II) shared by their erythrocytes and fixed tissues, including tumours, and it has been maintained that the genes determining the fate of transplanted tissues are identical with those determining the iso-antigenic differences. It was found also that agglutinins disappeared in the course of hyper-immunization against mouse leukaemia but were replaced by protective antibodies, indicating that two qualitatively different antibodies were directed against the same antigen. An analogy with the rhesus antigens which, in man, evoke two qualitatively distinct antibodies, namely, ordinary agglutinins and partial (blocking) antibodies, prompted an examination for similar antibodies in mice.

Antigenic materials from strain A mice were used to immunize mice of other strains, especially C57 blacks; the antigens comprised erythrocytes and two strain-A transplantable tumours, namely, C1300, a spindle-cell mammary carcinoma, and 15091a, a round-cell sarcoma, possibly a neuroblastoma. Three types of iso-antibodies were detected: (1) ordinary agglutinins; (2) agglutinins active only in the presence of normal serum; and (3) blocking antibodies demonstrable only by their power to inhibit agglutination. About 20% of normal C57 black mice carried antibodies of the second type which were evoked in other mice by relatively weak antigenic stimuli. These antibodies and the blocking antibodies persisted in the serum longer than did ordinary agglutinins. The responses to the two tumours differed in detail, possibly on account of the different proportions of antigens I and II which they carried. Each antigen appeared to have its own peculiarities in evoking antibodies which varied also with the method of administration of antigen and with the genetic constitution of the mice in which they were elicited. The effects of storage of antibody were very variable but in many of the more powerful hyperimmune sera, even when stored in the frozen state, agglutinins were gradually transformed into blocking antibodies. It is reasonable to suppose that the transformation would be greatly accelerated at the body temperature of mice and that, by analogy with iso-immunization in man, the blocking antibodies are of greater functional significance. Some transplanted tumours grow despite antigenic differences between transplant and host and then evoke antibodies. Some mice dying of such transplanted tumours had high titres of iso-antibodies and it is granted that factors other than antibodies may be important in determining the fate of transplanted tumours. *L. Foulds*

2062. **Degenerative Changes Induced in Tumor Cells by *Serratia marcescens* Polysaccharide**
I. C. DILLER. *Cancer Research* [*Cancer Res.*] 7, 605–626, Oct., 1947. 62 figs., 18 refs.

The destructive action of *Serratia marcescens* polysaccharide and other bacterial toxins on tumours has been attributed mainly to injury of blood vessels and haemorrhage. The present investigation indicates, in addition, a direct toxic action on tumour cells.

Mice bearing transplanted sarcoma 37 were used for most of the experiments. The polysaccharide (0·01 mg.) was injected intraperitoneally and mice were killed for cytological examination at intervals thereafter. The dose used killed 20 to 30% of the mice, usually within 24 hours, and destroyed about a quarter of the tumours. The cytological changes, which are described in detail and illustrated by photomicrographs and drawings, pointed to a relatively selective action on dividing cells. The first response, observed 1½ to 2 hours after an injection, consisted of swelling of prophase nuclei accompanied by blistering and other changes of the nuclear membrane. Subsequently the nuclear membrane col-

lapsed or nuclear contents were extruded. The degeneration of the cells initially affected reached a peak between 4 and 5 hours after an injection when the tumours were grossly haemorrhagic; swollen resting nuclei, blebbed prophase nuclei, bean-shaped shrunken nuclei, clumped metaphases, and extruded filaments were then present. The amount of destruction varied considerably; some tumours became almost completely necrotic in 6 hours. Inhibition of cell division did not last for more than 3 days. Between 72 and 96 hours after injection, morphologically unaltered resting nuclei resumed division and rapid proliferation of the tumour began. The onset of cell division was probably correlated with the restitution of an adequate blood supply. If no resting nuclei survived for 3 days, the tumour was no longer viable. Repetition of the treatment at 3-day intervals did not appreciably increase cell destruction and a growth, once re-established, was not noticeably impeded by further injections, indicating that either the tumour or the mouse became resistant to the bacterial agent. Injection directly into the substance of the tumour was ineffective. Normal tissues in which cell division or rapid nucleoprotein synthesis was in progress also responded to the polysaccharide but were much less sensitive than tumours, about ten times the dose being needed to produce comparable effects. Similar cellular changes, though less pronounced, were also found in spontaneous mammary tumours in rats and mice as well as in biopsy material from 16 patients treated with polysaccharide for sarcoma, but there only a relatively small amount of tissue was affected.

Injection of polysaccharide followed after 4½ hours by irradiation of the tumour with *x* rays destroyed about 75% of transplanted sarcomata in mice, whereas each treatment alone destroyed only about 25%. The combined effect was greater, therefore, than would be expected from a summation of the separate effects.

It is concluded that *S. marcescens* polysaccharide exerts a direct toxic action on tumour cells which is independent of the results of interference with the blood supply. Dividing cells are most sensitive to the action. The relative insensitivity of carcinoma is unexplained but may be due to the smaller content of dividing cells. The destructive action of polysaccharide on tumours is not attributed, however, exclusively to direct toxic action on tumour cells; the anoxia resulting from vascular stasis may contribute to the result even in early stages before gross haemorrhage is apparent. *L. Foulds*

2063. **Observations on the Nature of the Oestrous Cycle and on the Effect Upon it of the Milk Factor, in Mice of Two Inbred Strains, Differing in Mammary Cancer Incidence**

E. C. ARMSTRONG. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 59–69, March, 1948. 9 refs.

Daily vaginal smears were obtained by the platinum loop method from mice of four groups: (1) Twelve R3 mice with the normal supply of milk factor; 9 mice (69%) ultimately developed tumours. (2) Eleven R3 mice removed from their mothers within 12 hours after birth and foster-nursed by CBA females; 3 mice (27%) developed tumours attributed to milk factor received before the mice were removed from their mothers. (3) Ten CBA mice considered free from milk factor; none developed a tumour. (4) Twelve CBA mice foster-nursed from 3 to 12 hours after birth by R3 females; 6 mice (50%) developed tumours.

The mice were observed as virgins for periods of 56 to 137 days from weaning or canalization of the uterus. Then they were mated and each bore one or more litters. Observations were continued for periods of 47 to 163 days and vaginal smears were then examined for 7 to 21 days at 9 months and 12 months of age, and thereafter at monthly intervals. The results with statistical tests of significance are presented in tables.

Foster-nursing with consequent addition or deprivation of milk factor had no apparent influence on the sexual cycles but there were indications that certain features were characteristic for a particular strain and were genetically determined. The cycles were longer in R3 than in CBA mice but the duration of oestrus was the same. Atypical cycles were observed in each group. The R3 mice had more frequent and more prolonged pseudo-pregnancies than the CBA mice but fewer periods of prolonged oestrus. It is possible that the genital tract in the high-cancer strain (R3) was less sensitive than that in the low-cancer strain (CBA) both to oestrin and to the local irritation (supplied in the experiments by taking of repeated smears), which tends to cause cornification, whereas the hormonal reaction to a mechanical stimulus simulating copulation was more sensitive and the pseudo-pregnant state was consequently initiated more readily in R3 than in CBA mice. The menopause occurred later in R3 than in CBA mice. *L. Foulds*

2064. **Culture of Human Leukaemic Blood Cells *in vitro*; Technique and the Growth Curve**

F. W. GUNZ. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 29–41, March, 1948. 22 refs.

The technique described for the culture of human leukaemic blood cells was devised in order to test *in vitro* therapeutic measures, such as ionizing radiations and chemical agents. The cultures were made in tubes in a fluid medium containing Ringer's solution and reconstituted dried human plasma. Total, differential, and mitotic cell counts were made at intervals on 31 cultures of blood from 11 patients with chronic myeloid leukaemia. The rate of mitotic division increased rapidly during the first few hours of culture, reaching a maximum in the basic medium after about 8 hours. The number of mitoses increased considerably beyond the eighth hour, when rat embryonic extract was added to the medium, and reached a peak in between 24 and 36 hours. Since ionizing radiations and many chemotherapeutic agents act primarily on dividing cells, material for testing their action should contain the maximum number of dividing cells, and the addition of embryonic extract is therefore recommended for all cultures intended for such tests.

Cell maturation apparently occurred in the cultures, for the number of polymorphonuclear cells usually increased during the first 2 days and the increase could be attributed only to maturation of immature cells.

Decreases in the number of immature cells were attributed to the failure of proliferation to keep pace with maturation. Polymorphonuclear cells died from the earliest stages of culture. After the second day, maturation and the rate of proliferation of cells, decreasing rapidly during the second 24 hours of culture, had little influence on the growth curves, which henceforth were determined mainly by degenerative processes. In tests of therapeutic agents, therefore, no useful purpose is served by prolonging culture beyond 48 hours. *L. Foulds*

2065. **Culture of Human Leukaemic Blood Cells *in vitro*. Normal and Abnormal Cell Division and Maturation**
F. W. GUNZ. *British Journal of Cancer* [*Brit. J. Cancer*] **2**, 41–48, March, 1948. 27 figs., 19 refs.

Cytological examinations of the cultures, described in the preceding paper (Abstract 2064), of human blood cells from patients with chronic myeloid leukaemia are here reported. The life of the cultures was divided into two phases, a growth phase and a decay phase.

The growth phase covered the first 36 to 48 hours of culture and was characterized by proliferation of immature cells. Mitoses, though rare in the circulating blood, were regularly present in cultures from the second hour onwards. The proportions of the different stages of mitosis were not grossly abnormal, and, in particular, there was no evidence of metaphase arrest. The great majority of mitoses during the early growth phase were normal and no gross deviation from the haploid number of chromosomes was found. Minor irregularities of mitoses were seen occasionally and pyknotic mitoses were common in the later stages of the growth phase. Signs of limited maturation were often seen. As the growth phase progressed, more and more cells showed signs of abortive or abnormal maturation. It was concluded that immature cells proliferated by mitosis and underwent partial maturation. There was no evidence of amitosis and some polypoid cells were attributed to endomitosis. Abnormal "resting" cells were present even in the earliest stages of culture, increased during the later stages of the growth phase, and became very numerous in the decay phase. Either nucleus or cytoplasm might be involved and asynchronism between the two was common. The decay phase, characterized by degenerative changes and death of all cell types, extended for a variable period from the second day of culture. The last cell usually died between the sixth and ninth days of culture, but sometimes several days later. Abnormal resting cells became very numerous and monocytoid cells were frequent. *L. Foulds*

2066. **Influence of 2,3-Dimercapto Propanol (BAL) on the Induction of Skin Tumors in Mice by 3,4-Benzpyrene**
L. M. LUSKY, H. A. BRAUN, and G. WOODWARD. *Cancer Research* [*Cancer Res.*] **7**, 667–668, Oct., 1947. 1 fig., 4 refs.

It has been suggested that the first step in carcinogenesis by hydrocarbons is combination with –SH groups on the proteins of the cell. "If these free –SH groups have been previously blocked by an anticarcinogen or if the anticarcinogen competes with the carcinogen for cellular fixation, the carcinogen will be eliminated without producing its characteristic effects." BAL combines with compounds which attach themselves to –SH groups and should therefore interfere with the combination of carcinogen and tissue–SH since both BAL and tissue–SH would compete for hydrocarbon. Mice were painted with benzpyrene and on the next day with BAL in "carbowax". The results are shown below:

Treatment	No. of Mice at Start	No. which Survived 17 Weeks	No. with Tumours	Percentage with Tumours
Benzpyrene + 5% BAL in carbowax	55	40	23	57·5
Benzpyrene + carbowax	55	34	28	82·4
Benzpyrene alone ..	55	48	41	85·4

I. Hieger

2067. **Heterologous and Homologous Growth of Transplants During the Course of Development of Spontaneous Mammary Tumors in C3H Mice**
H. C. BROWNING. *Journal of the National Cancer Institute* [*J. nat. Cancer Inst.*] **8**, 173–189, Feb., 1948. 2 figs., 34 refs.

Spontaneous mammary tumours of C3H mice were transplanted into the anterior chambers of the eyes of mice. "Homotransplantation" was made into mice of the C3H strain and "heterotransplantation" into mice of other inbred strains, especially the C57 Black strain. [By established usage "heterotransplantation" indicates transfer to an alien *species*; its use for transfer to a different strain of the same species is confusing.] The tumours were classified according to their size into 5 stages of growth. The smallest tumours, 0·1 to 0·2 cm. in diameter, often regressed and histologically many of them were foci of squamous-cell metaplasia. No tumour larger than 0·2 cm. had that structure and none regressed. Multiple tumours were frequent and were found in 75% of the mice in which one tumour reached a size of 2 cm. or more. Up to 7 tumours were found in one mouse. The largest of the multiple tumours was almost always that which had appeared first. Metastasis occurred in 59% of mice with solitary tumours and 63% of those with multiple tumours when the sole or largest tumour measured 2 cm. or more.

Homotransplantation into the eyes of C3H mice was almost always successful except with the smallest tumours measuring 0·1 to 0·2 cm. Homotransplants always grew progressively and, if the mouse was allowed to survive, filled the anterior chamber, burst out of it, and grew unchecked in surrounding tissues. "Heterotransplants" in the eyes of mice of other strains never grew progressively; usually they grew for 10 to 12 days, with a peak at 8 days, and then regression began. The growth, to a varied extent, of the "heterotransplants" was used as an indicator of the degree of "autonomy" attained by the tumour whence they derived. On this assumption

" autonomy " of solitary tumours developed and increased with increasing age and size of the tumours and the rate of growth of homotransplants increased concurrently. In about a third of the cases in which 2 tumours from the same mouse were examined the relative degrees of autonomy corresponded with the relative sizes of the tumours, with the autonomy of solitary tumours of comparable age, and with the rapidity of growth of homotransplants. In the other two-thirds of cases of multiple tumours, the degree of autonomy was either about the same in the larger as in the smaller tumour or was greater in the smaller tumour whilst the correspondence between homotransplantation and heterotransplantation was less sharp or was lacking. It is suggested that a second tumour may usurp the autonomy of the first or that loss of autonomy by one tumour allows or encourages the development of a second neoplastic focus.

Material for transplantation was obtained by biopsy from 7 tumours; about three-quarters of the tumour was removed and after an interval the operation was repeated. An appreciable increase in autonomy and in the speed of growth of homotransplants was observed between the first and second tests on 2 tumours; in the other 5 tumours autonomy was not appreciably changed except that the capacity for heterologous and for homologous growth of one tumour seemed to decrease between the tests.

Old animals were less receptive to heterotransplants than younger ones, but sex and the presence of milk factor seemed unimportant. Saline suspensions of tumours injected into the eye did not grow, but the eyes were resistant to subsequent implantation of fragments. It was deduced that immunity was provoked even by unsuccessful heterotransplantation, that the anterior chamber of the eye participated in immune reactions, and, further, that autonomy depended not on a failure to provoke immune reactions but on a positive growth energy. Neither autonomy nor speed of homologous growth was correlated with histological structure; this is in accordance with the view that autonomy is not related to anaplasia or other morphological features.

[The abstracter does not accept the assumption that the ability to grow in the eyes of another kind of mouse is a measure of the " autonomy " of a tumour.]

L. Foulds

2068. **The Effect of Folic Acid and its Antagonists on Rous Chicken Sarcoma**

P. A. LITTLE, A. SAMPATH, V. PAGANELLI, E. LOCKE, and Y. SUBBAROW. *Transactions of the New York Academy of Sciences* [*Trans. N.Y. Acad. Sci.*] **10**, 91–98, Jan., 1948. 1 fig., 4 refs.

The Rous sarcoma was transmitted by injections of aqueous suspensions of frozen tumour. A synthetic diet free from folic acid completely prevented the development of tumours in baby chicks, although nearly all developed tumours when the diet was supplemented by daily injections of folic acid. N-methylfolic acid, pteroyldiglutamic acid, and pteroyltriglutamic acid were equivalent to folic acid in furthering tumour development; pteroylaspartic acid, pteroic acid, and *p*-aminobenzoyl-triglutamic acid had no comparable effect. In chickens maintained on a normal diet the development of tumours was inhibited by administration of various folic acid antagonists (4-amino-folic acid, 4-amino-folic acid with *d*(-)glutamic acid, and 4-amino-pteroylaspartic acid). After tumours had begun to grow in adult birds, administration of folic acid antagonists inhibited further growth. It is suggested that folic acid forms the prosthetic group of an enzyme necessary for the " metabolism " of the virus of Rous sarcoma. *L. Foulds*

2069. **The Rous Chicken Sarcoma in Birds Treated with Folic Acid and its Derivatives: A Pathological Study**

E. WOLL. *Transactions of the New York Academy of Sciences* [*Trans. N.Y. Acad. Sci.*] **10**, 83–91, Jan., 1948. 12 figs., 13 refs.

Observations are recorded on the naked-eye and microscopical appearances of Rous sarcoma in 350 chickens of ages ranging from 2 days to 10 weeks, some of which were treated with folic acid or its derivatives. Attention is drawn to the differences between slowly-growing and rapidly-growing tumours. The whole range of these differences was seen in both treated and untreated birds, no distinctive pattern or cytological detail being specific to either group though the author formed the impression that tumours inhibited by treatment showed more cytological degeneration and, possibly, disruption of mitotic figures. [The additions to the pathology of the Rous sarcoma provided in this report are inconsiderable.] *L. Foulds*

2070. **Effects of Alloxan upon Function and Structure of Normal and Neoplastic Pancreatic Islet Cells in Man**

J. W. CONN and D. L. HINERMAN. *American Journal of Pathology* [*Amer. J. Path.*] **24**, 429–449, March, 1948. 7 figs., 43 refs.

A case of organic hyperinsulinism was observed over a period of 193 days. During the " pre-alloxan period " (35 days) numerous investigations of metabolism were carried out. The average fasting blood sugar was 31 mg. per 100 ml.; carbohydrate tolerance was high. During the " alloxan period " (9 days) a total of 60 mg. of alloxan was given intravenously (800 mg. per kilo body weight) without untoward reaction. In the " post-alloxan period ", over the first 15 days the fasting blood sugar averaged 45 mg. per 100 ml., carbohydrate tolerance had decreased, but severe hypoglycaemia before breakfast persisted. An islet-cell adenoma of the pancreas was removed surgically. Frank diabetes mellitus then developed, requiring vigorous insulin therapy, which was gradually reduced and stopped. Finally, the fasting blood sugar became consistently normal, but glucose tolerance curves of plateau type persisted. Serial curves suggested that normal carbohydrate tolerance would eventually return.

Elaborate histological studies were made on the tumour and the normal pancreas. The tumour conformed to the usual descriptions. In many places the tumour cells were continuous with ductule epithelium. The majority of the tumour cells resembled β cells. In

the tumour there was no evidence of alloxan injury. In contrast the normal pancreas showed severe alloxan injury; 96% of β cells had degenerated or disappeared, and 15% of islets were completely destroyed; 7% of islets were hyperplastic, and 90% of the cells in them were α and δ cells.

It is concluded that the normal pancreatic islet cells of man are not resistant to alloxan, in contrast to the view generally held. On the other hand the cells of human islet adenomata are very resistant to alloxan, probably because their metabolism is different from that of normal islet cells. *R. R. Wilson*

CLINICAL PATHOLOGY

2071. **Cytological Findings in Exudates and Transudates.** [In English]
G. WIHMAN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 87–97, 1948. 17 figs.

The author's method consists of centrifuging the exudate and transferring the sediment by means of a funnel into a raw sausage skin, drawn together at the lower end. The skin is then placed in a centrifuge tube, partly filled with water, and is hung there by catching the upper end of the skin between the orifice of the tube and a rubber bung. After centrifugation, the skin containing the concentrated exudate is removed and tied just above the sediment. The whole sediment is thus collected, and since it and the sausage skin both consist of animal tissue, they can be fixed, processed, and blocked in paraffin in the usual way. Another method is to fix the sausage skin to the stem of a filter funnel. The sediment from the centrifuged exudate, together with a small quantity of the supernatant, is then poured into the funnel and drops into the sausage skin, which is hanging from the funnel like the finger of a glove. The skin is tied off above the sediment and the superfluous material is cut off. Fixation, dehydration, and embedding are then carried out as usual. *R. B. Lucas*

2072. **The Effect of Surgical Operations on the Bromsulfalein-retention Test**
H. J. TAGNON, G. F. ROBBINS, and M. P. NICHOLS. *New England Journal of Medicine* [*New Engl. J. Med.*] **238**, 556–560, April 15, 1948. 9 refs.

This report, from the Memorial Hospital for the Treatment of Cancer and Allied Disorders, New York, deals with 20 patients undergoing operations other than abdominal. The absence of pre-existing liver disease among these patients was determined by clinical examination only. The bromsulphalein-retention, thymol turbidity, and cephalin flocculation tests were carried out before operation, immediately after the operation, and again later in convalescence. The two last tests revealed no significant change throughout; but in 14 of the 20 patients the bromsulphalein test showed temporary significant retention of the dye over a period of days before returning to normal. There appeared to be a correlation between the severity of the operation and retention of the dye. The mechanism of this phenomenon is unknown, though the authors speculate on a possible transient liver anoxia and on the effects of "pentothal" and ether. *R. N. Johnston*

2073. **Depression of the Exogenous Creatinine/Insulin or Thiosulfate Clearance Ratios in Man by Diodrast and *p*-Aminohippuric Acid**
B. CRAWFORD. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 171–175, March, 1948. 38 refs.

It is confirmed that in normal man the exogenous creatinine clearance exceeds the simultaneous inulin or thiosulfate clearance to an extent clearly beyond the limits of experimental error. In 39 periods in 7 subjects, the thiosulfate/inulin clearance ratio averages 0·98, confirming the conclusion of Newman, Gilman, and Phillips that the thiosulfate clearance is at the level of glomerular filtration.

The administration of large doses of "diodrast" or PAH (substances known to be copiously excreted by the renal tubules in man) depresses the creatinine/inulin and creatinine/thiosulfate ratio to or towards 1·0. These facts are presented as new evidence for the tubular excretion of exogenous creatinine, and confirm the belief that in man as in other mammals the inulin clearance is at the level of glomerular filtration.—[Author's summary.]

MORBID ANATOMY

2074. **Pathological Histology of the Nerve Endings in the Carotid Body.** (Zur Pathohistologie der Nervenendigungen im Glomus caroticum)
J. MEYER-ARENDT. *Frankfurter Zeitschrift für Pathologie* [*Frankfurt. Z. Path.*] **59**, 389–397, 1948. 6 figs., bibliography.

Four kinds of endings of nerve fibres in the carotid body are described: the end-clubs (chiefly combined with varicosities of the fibres), the end-loops, the terminal reticulum, and (not previously described) complicated multicellular end-bodies with enveloping plasmodia, similar to the Vater–Pacini bodies. Pathological changes observed in the ectodermal-nervous portion of the organ include infiltration with round cells, inflammation, cirrhosis, amyloid and hyaline degeneration and arteriosclerosis. *O. Neubauer*

2075. **Laennec Cirrhosis. Its Histiogenesis, with Special Reference to the Role of Angiogenesis**
E. MOSCHCOWITZ. *Archives of Pathology* [*Arch. Path.*] **45**, 187–215, Feb., 1948. 27 figs., bibliography.

Particular attention is paid in this paper to the vascular component of the cirrhotic process. Some 75 livers in which all stages of the disease were present were studied, and in 8 of these serial sections were examined. On the basis of comparisons with embryological "angiogenesis" it was decided that new capillary formation was essentially autochthonous; in serial sections these capillaries were found to persist, sometimes maturing into venules

to form a direct communication between portal and hepatic venous radicles, usually along interlobular septa in company with the fibrous tissue, but occasionally across a lobule. No evidence of increased arterial supply was found in the granulomatous tissue. The author also discusses the question of bile-duct proliferation and recognizes three types of new bile channel, but there was no evidence of liver cell formation from bile-duct epithelium. *W. S. Killpack*

2076. **Spread of Carcinoma to the Spleen. Its Relation to Generalized Carcinomatous Spread**
J. W. HARMAN and P. DACORSO. *Archives of Pathology* [*Arch. Path.*] **45**, 179–186, Feb., 1948. 30 refs.

In this rather novel survey, out of 116 cases of carcinoma studied at necropsy 30 were selected in which there was a strong tendency towards generalized invasion of the body, metastases having been found in organs in different body cavities. Cases in which tumour spread appeared to have been arrested by regional barriers or to have been halted in the pulmonary capillary bed were however excluded. At 9 necropsies metastases were visible in the spleen, and to these a further 6 cases were added in which microscopical metastases were discovered, giving a total incidence of 50%. Other organs in which nearly half the secondary deposits escaped naked-eye detection were: lungs, spleen, pancreas, heart, and bone marrow. Other figures of interest are given concerning metastasis to other organs. *W. S. Killpack*

2077. **Chronic Granulomas in the Alimentary Tract Caused by Minute Mineral Particles. II. "Boeck's Disease" and Occurrence of Minute Mineral Particles. (Preliminary Report.)** [In English.]
O. REFVEM. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 107–121, 1948. 7 figs., 11 refs.

Sections from 209 cases of alimentary tract lesions were examined with a view to determining whether the presence of foreign bodies acted as an aetiological factor in certain chronic inflammatory conditions, including foreign-body granuloma, granulation tissue, subacute and chronic non-specific inflammation, and conditions regarded as definite tuberculosis, mainly in the ileo-caecal and ano-rectal regions. The sections were strained by Masson's method, and were also examined under the polarizing microscope, the nature of any foreign body being deduced from its refractive properties.

Foreign bodies were considered to have been detected with certainty in 53 of the 209 cases. The highest percentage was in the ano-rectal region, foreign bodies being found in 34% of the specimens and talcum representing 85% of all foreign bodies found. In 2 out of 34 cases of ileo-caecal tuberculosis it was considered that the diagnosis should have been one of foreign-body granuloma. The presence of talcum in the anal lesions is ascribed to deposition of this material in the course of digital examination. In 4 out of 9 cases of abdominal fistula and in 6 out of 8 cases of peritoneal adhesions talcum was also found. In a control examination of material from 50 cases of Hodgkin's disease foreign bodies could not be demonstrated.

Sections from about 100 cases diagnosed as Boeck's disease were also examined by polarized light. In 4 cases crystalline material was found in the nodules, and it is suggested that certain cases histologically similar to Boeck's sarcoid may be examples of a more or less generalized foreign-body reaction. *R. B. Lucas*

2078. **Islets of Langerhans in Fibrocystic Disease of the Pancreas. A Hitherto Undescribed Abnormality?** [In English]
O. TORGERSEN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 124–130, 1948. 6 figs., 13 refs.

Five cases of fibrocystic disease of the pancreas are described in which lesions of the islets were present, the patients being children aged from 2 months to 2 years. Clinically, there had been vomiting, failure to gain weight, and loose and fatty stools. The changes in the pancreas, apart from the islets, conformed to those already seen in fibrocystic disease. The islets, however, showed definite changes not previously reported. In number they appeared normal, but many of them contained one or more duct-like structures lined by epithelium. In some this epithelium was of the tall columnar type and closely resembled small pancreatic ducts, though more often the ducts were less conspicuous, being cleft-like and lined by stratified epithelium. In other cases the ducts were wider and the epithelium showed degenerative changes. Serial sections revealed a connexion between these ducts and the excretory ducts of the pancreas. The author thinks that these ducts may be related to the small tubules demonstrated in the guinea-pig by Bensley (*Amer. J. Anat.*, 1911), and that in man, in fibrocystic disease, they persist into post-foetal life.
R. B. Lucas

2079. **Investigations on the Pathology of the Pancreas in the First Year of Life, with Special Reference to the Connective Tissue.** (Untersuchungen zur Pathologie des Pankreas im ersten Lebensjahr unter besonderer Berücksichtigung des Bindegewebes)
G. ULE. *Frankfurter Zeitschrift für Pathologie* [*Frankfurt. Z. Path.*] **59**, 359–380, 1948. 4 figs., 19 refs.

In 72 premature infants and infants within the first year of life, the weight and length of the pancreas differed greatly, without definite relation to age. The average weight in newborn infants is 3·07 g. The pancreas at this age is very rich in connective tissue; this is apparently connected with the special function of connective tissue in foetal life; signs of embryonal haematopoiesis were frequently seen. There is a relative insufficiency of the pancreas at this age which may be responsible for certain disturbances. In cases of general infection hyperaemia was repeatedly found, and in 3 cases haemorrhages were seen. Cases are described in which severe alterations (phlegmonous pancreatitis, obstruction of duct) had occurred without corresponding clinical signs *in vivo*. *O. Neubauer*

Microbiology

VIRUSES

2080. **Studies on Vaccinia Haemagglutinin. I. Some Physico-chemical Properties**
C. M. CHU. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 42–48, March, 1948. 1 fig., 15 refs.

These observations confirm and extend those originally made by Australian workers. Vaccinia haemagglutinin (V.H.) was found in virus preparations from rabbit tissues and skin, sheep lymph, and chick embryos (chorio-allantois). Calf lymph, found by other workers to be inactive, was not tested. Only susceptible fowl cells were agglutinated. Centrifugation showed V.H. to be dissociable from the virus particles, although it appeared to be more than a soluble antigen, because a purified suspension of elementary bodies had some agglutinating activity even after several washings.

Filtration experiments with " gradocol " membranes gave a filtration end-point between 230 and 310 mμ, but results were unsatisfactory because of strong absorption on to the filters. High speed centrifugation studies with both rabbit skin and chorio-allantoic preparations suggested that V.H. consisted of uniform particles of 65 mμ. V.H. was remarkably thermostable, withstanding boiling in a water-bath for several minutes but being destroyed by autoclaving. It was stable between *p*H 6·0 and 10·0. Attempts to isolate and purify it were not successful but yielded some useful information. V.H. was not soluble in ether, although lecithin and tissue lipids, which gave non-specific haemagglutination, were dissolved. It could be precipitated by 50% saturation with ammonium sulphate and by dialysis against distilled water, but the precipitate resisted redispersal. It could be absorbed on to kaolin at *p*H 6·0 and eluted at *p*H 10·0.

It was confirmed that a similar agglutination of susceptible fowl cells is produced by lecithin, trypsin and some filtrates of cultures of *Vibrio cholerae*.

D. G. ff. Edward

2081. **Studies on Vaccinia Haemagglutinin. II. Some Immunological Properties**
C. M. CHU. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 49–59, March, 1948. 3 figs., 25 refs.

Rabbits, infected with vaccinia, developed anti-vaccinia haemagglutinin antibodies (anti-V.H.). Repeated observations showed that over a period of months titres of the antibodies varied, but that whereas the agglutinin, precipitin, and complement-fixing antibodies varied proportionately with each other, the anti-V.H. behaved independently. Anti-V.H. was absent from normal rabbit sera and from other normal human and animal sera, except for one sample of horse serum. It was stable at 70°, but destroyed at 80° C. It was contained in the globulin fraction of serum (chiefly in the pseudo-globulin).

If in a haemagglutinin-inhibition test the antigen-antibody mixture was incubated for up to 3 hours before addition of the red cells higher titres were obtained. Vaccinia haemagglutinin (V.H.) can be recovered from a neutral mixture with antibody by heating to 100° C., because of its stability at this temperature. Agglutinated erythrocytes were rendered stable again by treatment with antibody; V.H. actually eluted and combined with antibody. Combination of V.H. with anti-V.H. did not fix complement. V.H. itself had little or no precipitating or complement-fixing properties and appeared to be distinct from the L–S antigen. This was confirmed in absorption experiments. Absorption of an antivaccinia serum with washed elementary bodies free from V.H. removed both agglutinin and neutralizing antibodies, but left anti-V.H. intact. Absorption with L–S removed the agglutinin but not the neutralizing antibody or anti-V.H. Absorption, carried out with V.H. adsorbed on fowl erythrocytes, reduced the titre of anti-V.H. but did not affect the agglutinin.

It was concluded that V.H. and L–S were distinct antigens and that, although absorption with V.H. removed some neutralizing antibody, V.H. and neutralizing antigen were also distinct. V.H. is possibly a virus–host interaction product.

D. G. ff. Edward

BACTERIA

2082. **Capsular Antigens in Some Non-haemolytic Streptococci Belonging to the Lancefield Group D.** [In English]
K. SKADHAUGE. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 308–318, 1948. 7 figs., 16 refs.

The author notes that there is very little information in the literature about the presence of capsules in non-haemolytic streptococci. In the course of his own investigation into the serology of the enterococci he observed that capsular swelling occurred not infrequently. He discusses the various criteria on which the enterococci can be classified into *Streptococcus faecalis*, *Str. liquefaciens*, *Str. zymogenes*, and *Str. durans*, but remarks that in recent years the term enterococcus has been regarded as synonymous with Group D streptococcus.

In all, 12 strains showing capsular swelling with the homologous antiserum were recovered from infected appendices or human faeces. On blood agar they showed alpha haemolysis, none of the strains liquefied gelatin, and all strains grew in broth at 10° and 45° C. while 9 out of 12 were able to grow at 50° C. All strains survived heating at 61° C. for 30 minutes; 5 even resisted heating to 65° C. for the same time. Reduction in milk media was weak or absent. Further, in the fermentation tests none of the strains acted on sorbitol.

In the serological examination of the strains with sera of Lancefield's groups A, B, C, D, E, F, G, H, and K positive precipitation tests were only obtained with group D. With antisera prepared for all 12 strains the agglutination tests showed little or no cross-agglutination between one strain and another, and capsular swelling could only be demonstrated in each case by the use of the homologous serum. The capsule could best be demonstrated by staining with concentrated fuchsin solution to which the homologous serum had been added. Absorption tests carried out with a strain and its homologous serum showed that in some instances the antibody causing swelling was completely removed. *J. Smith*

2083. **Massive Colony Formation of *Bacterium friedländeri* in the Liver in Agranulocytosis**

J. I. DAVIDSON. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 51–66, Jan., 1948. 4 figs., 3 refs.

A common cause of death in agranulocytosis is bacterial invasion of the tissues. Where the course of the disease is most rapid the bacteriological findings may not be of great interest, but in those cases in which the progress of the disease is slower the ante-mortem multiplication of the invading bacteria may be remarkable. Such a case is described in which the liver presented a curious picture. Scattered throughout the surface and deep in the substance of the organ were numbers of spherical firm white areas about 5 mm. in diameter. Further investigation showed that these areas consisted of capsulated Gram-negative bacilli or bacteria suspended in a mucoid substance. Fresh material was not available for cultural identification, but the organism had the morphological characters of *Bacterium friedländeri*. The lung was extensively consolidated and over large areas the alveoli were packed with these capsulated Gram-negative bacilli.

[The lung lesions do not appear to have been quite those of the typical Friedländer pneumonia, but rather a generalized infection with an organism of the Friedländer type. Sufficient evidence has been brought forward to conclude that the bacterial colonies in the liver, at least, began to develop during the life of the patient.] *H. J. Bensted*

2084. **The Enhancement of Bacterial Infections by Adrenaline**

D. G. EVANS, A. A. MILES, and J. S. F. NIVEN. *British Journal of Experimental Pathology* [*Brit. J. exp. Pathol.*] **29**, 20–39, Feb., 1948. 4 figs., 19 refs.

Adrenaline increases the susceptibility of animal tissues to many bacterial infections. In intracutaneous tests in guinea-pigs the addition of 2 μg. of adrenaline to the inoculum caused an enhancement of the local infection as measured by size of lesion and minimal effective dose of bacteria, the enhancement being 100,000-fold in the case of *Clostridium septicum* and *Cl. welchii*. Not all clostridial infections were enhanced. *Haemophilus pertussis* infections in the rabbit were not enhanced. Among the organisms tested infectivity of *Proteus vulgaris* and *Streptococcus pyogenes* was enhanced 1,000-fold and of *B. subtilis* and *Staphylococcus aureus* 10-fold. The increased susceptibility of the tissues to these and certain other infections was confirmed in intramuscular tests. Susceptibility to infection with influenza A virus given intranasally and pneumococci injected intraperitoneally was not increased.

Lesions due to toxins were enhanced but to a lesser extent. The adrenaline effect appeared to be mostly upon infection as distinct from intoxication with substances in the inocula. Experiments were performed to determine the mechanism by which the adrenaline acted.

The adrenaline was only effective when injected together with the organisms or during the subsequent 2 hours while vasoconstriction persisted. Adrenaline inhibited the exudation into tissues normally produced by histamine and bacterial toxins. Diapedesis of leucocytes was inhibited. Decolorization of methylene blue injected into the tissues with the adrenaline showed that the latter lowered the Eh of the tissues. Solutions of adrenaline formed a precipitate with tissue extracts; precipitation of tissue fluids and consequent entrainment of bacteria may help to explain fixation of bacteria in tissues in the presence of adrenaline.

Dyes tended to be fixed in skin treated with adrenaline. Bacteria appeared to be similarly fixed, but the experiments were complicated by the bactericidal action of normal serum for many organisms. Diminution of the exudate containing normal bactericidal substances in the presence of adrenaline and local fixation of the organisms instead of the normal rapid dispersal probably form part of the adrenaline effect. Physiological concentrations of adrenaline within the body are unlikely to effect susceptibility to infection under natural conditions. Adrenaline is only effective when injected into relatively dense tissues. Its effect was studied with a view to its use in increasing susceptibility under experimental conditions for feebly pathogenic organisms.

D. G. ff. Edward

2085. **Bacterial Lysis and Antiseptics**

R. J. V. PULVERTAFT and G. D. LUMB. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 62–64, March, 1948. 6 refs.

Lysis is produced in young broth cultures of bacteria by certain bactericidal agents. Organisms which are very susceptible to lysis are staphylococci, pneumococci, *Bacillus subtilis* and *Bacterium coli*; *Shigella dysenteriae* is less susceptible, and haemolytic and non-haemolytic streptococci are only slightly so. Concentrations of formalin, phenol, mercuric chloride, sodium hypochlorite, and " merthiolate " equal to about double the minimal bacteriostatic concentration produced lysis. Lysis did not occur with much higher concentrations of the first three antiseptics, although it was produced by all the concentrations of merthiolate tested, as well as by a wide range of concentrations of penicillin. Boric acid and " sulphamezathine " did not produce lysis. Antiseptics were added to broth cultures in the logarithmic stage of growth. Cultures at 24 hours' growth or cultures killed by heating were not subject to lysis. Lysis could be observed and measured by a number of different

methods; an excellent picture was afforded by stained films of organisms collected by centrifugation.

No lytic agent was present in filtrates of the cultures. Lysis appeared to be due to action of autolytic enzymes. An antiseptic may kill an organism by interference with certain enzyme systems, but may not interfere with the autolytic enzymes. Higher concentrations of certain antiseptics may destroy autolytic enzymes in addition and thus prevent lysis. *D. G. ff. Edward*

2086. **Investigations on the Typing of Staphylococci by Means of Bacteriophage. I. The Origin and Nature of Lysogenic Strains. II. The Significance of Lysogenic Strains in Staphylococcal Type Designation**
H. W. SMITH. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 74–81, and 82–89, March, 1948. 13 refs.

As a high proportion of strains of *Staphylococcus aureus* isolated from cattle are susceptible to one phage (42D), an attempt was made to differentiate between them. Seven out of 23 type-42D strains carried a phage lysogenic for other strains of the group. None were lysed by phages active for other types of staphylococci.

A 42D phage filtrate lysed non-lysogenic strains to full titre but lysogenic strains only to a partial titre. The propagating strain for the phage itself was only acted upon to a partial titre but a higher titre was obtained after further adaptation. Certain other strains which could not be typed by the ordinary method were also lysed to a partial titre. Seven phages (5 obtained from lysogenic group 42D strains and 2 from adapted strains), shown by cross-resistance tests to be different, were titrated against a number of 42D strains and also against other untypable strains shown to be lysogenic for group 42D strains. The lysogenic strains could be divided into 9 phage types according to the pattern of their reactions, thus allowing a sub-division of the 42D group. The non-lysogenic strains were susceptible to all the test phages. Typing depended on acquired phage resistance of the lysogenic strains. Out of 200 strains of coagulase-positive staphylococci isolated from cattle 93 were of group 42D and of these 47 were lysogenic. There were also 62 untypable strains; 47 were susceptible to the test phages and thus their inability to be typed depended on acquired phage resistance.

In an investigation of strains isolated from sheep which belonged to another phage type lysogenic strains were also demonstrated and difficulty of typing was shown to be due to acquired resistance. Certain of the strains used to propagate the routine type phages were found to be lysogenic. Most strains of staphylococci made resistant to a phage were shown to be carrying that phage. In the use of strains made resistant to two different phages either one or both phages could be demonstrated.

In the second paper it is shown that the various subtypes in phage types 1, 2, and 3 (Wilson and Atkinson) are due to the fact that the majority of the strains are lysogenic and to the occurrence of acquired phage resistance. A classification is suggested of what are conveniently called genetic types, independent of acquired phage resistance. Lysogenic strains with acquired resistance, and resistant variants of non-lysogenic strains, retained their properties unaltered after a year's maintenance in the laboratory.

When two strains of staphylococci were cultured together in broth, one strain being non-lysogenic and the other lysogenic for the former, only organisms of the lysogenic phage types could eventually be isolated from the mixture. From similar mixtures of two strains lysogenic for each other only organisms of a new phage type, which was a resistant variant of one of them, were isolated. In the course of an examination of many strains of staphylococci isolated from milk samples from one herd evidence was obtained that such resistant variants might be found in the field. The epidemiological significance of the findings is discussed with particular reference to different sub-types developing under field conditions when observations are extended over a prolonged period. The results suggest that it is important to isolate strains directly on plates and not after previous incubation in broth. *D. G. ff. Edward*

2087. **The Biochemistry of Bacterial Toxins. 2. The Enzymic Specificity of *Clostridium welchii* Lecithinase**
M. G. MACFARLANE. *Biochemical Journal* [*Biochem. J.*] **42**, 587–590, 1948. 3 refs.

Lecithinase activity has previously been demonstrated in *Clostridium welchii* toxin. Tests for enzymic hydrolysis of other phosphorus compounds, by methods previously described, showed that crude sphingomyelin was hydrolysed to the extent of 70%, but more slowly than lecithin. The hydrolysis, like that of lecithin, was activated by calcium ions and inhibited by sodium fluoride. The products of hydrolysis were phosphorylcholine and a phosphorus-free compound approximating in composition to lignocerylsphingosine. Neither phosphatidylethanolamine nor phosphatidylserine (the " kephalin " fraction from sheep brain) was hydrolysed. *P. B. Marshall*

2088. **The Biochemistry of Bacterial Toxins. 3. The Identification and Immunological Relations of Lecithinases Present in *Clostridium oedematiens* and *Clostridium sordellii* Toxins**
M. G. MACFARLANE. *Biochemical Journal* [*Biochem. J.*] **42**, 590–595, 1948. 11 refs.

In toxins from strains of *Clostridium oedematiens* and *Cl. sordellii*, lecithinase activity was determined by estimation of acid-soluble phosphorus liberated from lecithin, and the lecitho-vitellin (L.V.) factor by the development of turbidity in a clear emulsion of egg yolk. Analyses of the products of the reactions were carried out. *Cl. oedematiens* type-A toxin contained two lipolytic enzymes, a lecithinase (γ-toxin) similar in action to *Cl. oedematiens* β-toxin and to *Cl. welchii* α-toxin, and a lipase splitting off fatty acids, while type-B toxin contained lecithinase only. This is consistent with the morphological appearances of these strains in plate tests, since type-B strain does not produce the " pearly layer " on the surface of the culture which is characteristic of type A. The lipase of type-A toxin is probably the same factor as

Oakley's ϵ-toxin. The action of *Cl. oedematiens* lecithinase (β-toxin) was optimal over a *p*H range of 6·0 to 7·6 and its activity was increased by calcium chloride and inhibited by sodium fluoride. *Cl. oedematiens* toxin had a much lower lecithinase activity than had *Cl. welchii* toxin, and type-A toxins had less activity than type B.

Determinations of antilecithinase activity by antitoxic sera showed that, while there was little inhibition of β-lecithinase by type-A serum, there was complete inhibition of γ-lecithinase by type-B (Todd 3) if sufficient serum was added. This apparent cross-reaction was explained by the fact that all the horses from which the sera were prepared received a preparatory dose of alum-precipitated toxoid from a type-A (γ-toxin) filtrate. It was finally concluded that lecithinase activity in the various types of toxins was inhibited by a homologous, but not by a heterologous, antitoxic serum, and that type-A and type-B lecithinase were probably identical respectively with the γ- and β-toxins of *Cl. oedematiens*.

In *Cl. sordellii* filtrates, lecithinase activity was lower than the L.V. value, suggesting the presence of a second factor affecting egg yolk. This toxin may contain an enzyme attacking the yolk protein, thereby affecting the turbidity development in the L.V. test, but it is more probable that it contains a lipase similar to that of *Cl. oedematiens* type A, since cultures of *Cl. sordellii* showed the "pearly layer". The products of hydrolysis of lecithin were not identified, but the reaction is probably similar to that of *Cl. welchii*. An inhibition of 50 to 100% of the L.V. reaction was obtained with both *Cl. welchii* and *Cl. oedematiens* antitoxic sera (*Cl. sordellii* antitoxins being unobtainable). Further work on the purification of *Cl. sordellii* lecithinase is necessary before the inhibitory action of antitoxins can be tested on this enzyme. *P. B. Marshall*

2089. **A New Mycobacterial Infection in Man. I. Clinical Aspects. II. Experimental Investigations in Laboratory Animals. III. Pathology of the Experimental Lesions in the Rat. IV. Cultivation of the New Mycobacterium**

P. MacCallum, J. C. Tolhurst, G. Buckle, and H. A. Sissons. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 93–122, Jan., 1948. 18 figs., 38 refs.

In 1940, in the district of Bairnsdale, Victoria, in a boy of 2½ years an ulcer developed in the skin of the leg, the marginal tissues of which were found to be teeming with acid-fast bacilli morphologically indistinguishable from tubercle bacilli. Histological and cultural methods failed to confirm this identity. The tissue reactions were not typical of tuberculous infection, the organism would not grow on laboratory media under conditions suitable for the cultivation of *Mycobacterium tuberculosis*, and inoculation into the usual laboratory animals was not followed by any obvious infection. The ulceration in the skin of the patient was of a progressive nature lasting for about 6 months. An unexplained deterioration set in and the child died without an immediate cause of death being revealed.

Since 1940 there have been four similar cases from the same area and a further one from a district some 200 miles distant. These cases all commenced with a small abrasion or insect bite either on the shin or on the forearm—usually the former. Except for the first case the condition cleared up after the application of bland lotions, wide excision of the ulcerated areas and skin-grafting. Nevertheless, the total duration of the disease, with the exception of the last case (4 months), was on an average 16 months. Leprosy was excluded on clinical grounds and the ultimate success achieved in the cultivation of the infecting organism would appear to substantiate such conclusions.

The inoculation of ground-up tissue from the third patient into a rat resulted in the death of this animal some 13 months later, but the only lesion found in the animal was a small nodule in the inguinal region at the site of the inoculation, containing acid-fast bacilli, and attempts at passage of this material failed. Another rat inoculated intraperitoneally with pus from the same patient died in 4 months, the lungs containing many acid-fast bacilli. A saline extract of the lung tissue was injected intraperitoneally into another rat and 9 months later the abdomen of this animal became visibly distended. When it was killed about 50 ml. of peritoneal fluid, teeming with acid-fast bacilli, was recovered. Passage experiments from then onward were fairly successful—even to the extent of producing ulcerated skin lesions crowded with acid-fast bacilli. The most characteristic lesion in male rats inoculated intraperitoneally was swelling of the scrotum after an average of about 4 months with fixation of the testes due to an early reaction in the epididymis. Ascites developed later and in some cases the whole of the posterior part of the animal became oedematous and ulcerative. The rats died about 1 year after inoculation.

Mice were also successfully inoculated, but there was a latent period of 3 to 6 months before the swelling of the subcutaneous tissues and the abdomen began, and gross subcutaneous oedema was more common. Occasionally small lesions of a non-progressive or self-healing nature were noted in guinea-pigs, rabbits, fowls, and lizards. The most remarkable features of the pathology, as seen in the rat, were the long latent period, the regularity of the epididymal involvement, and the great exudation of fluid—up to 200 ml. The actual type of cellular reaction was not so distinctive.

The early failures to cultivate the new mycobacterium in the laboratory were due to the very restricted temperature requirements for growth. The optimum temperature proved to be 33° C.; above 37° and below 25° C. growth could not be demonstrated. Egg-yolk agar and Petragnani's media were the most suitable for the cultivation of the organism. Visible colonies developed in about 4 weeks in primary culture and about 2 weeks in secondary culture. The young colonies were transparent, smooth, and dome-shaped, but the fully grown colonial forms varied somewhat according to the medium employed. Generally they were opaque and only slightly convex or even flatter. Suspensions of these cultures reproduced the complete course of the disease in rats. The organism was killed by heating to 60° C. for 30 minutes. It is concluded that the new mycobacterium,

which has not yet been named, was the true cause of the condition described in the 6 human cases; infection would seem to have been caused by inoculation of the organism at the site of the initial lesion, but the agent has yet to be discovered. *H. J. Bensted*

IMMUNITY

2090. **Serological Differentiation of Lipids from Ox Brain.** (Über die serologische Differenzierung von Lipoiden aus Rinderhirn)
F. HEIMANN and A. KLOPSTOCK. *Schweizerische Zeitschrift für Pathologie und Bakteriologie* [*Schweiz. Z. Path. Bakt.*] **11**, 11–24, 1948. 13 refs.

Injection of lipids (lecithin, cephalin, sphingomyelin) treated with pig serum into rabbits resulted in the production of complement-deviating antibodies. Anti-lecithin sera were the weakest; anti-Merck-lecithin sera reacted more strongly with Merck-lecithin than with brain lipids. Anti-brain-lecithin-sera gave no reaction with Merck-lecithin. Antisphingomyelin sera reacted more strongly with sphingomyelin than with brain-lecithin or cephalin.
C. L. Oakley

2091. **The Antibody Response in Cases of Radiation Lymphopenia and in the Reticuloses**
R. W. EVANS. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 123–130, Jan., 1948. 13 refs.

With a suspension of *Salmonella paratyphi* A (H) as antigen, the author examined the antibody response in 30 patients with a lymphopenia due to radiation therapy, and in a control group of 17 normal individuals. There was a delay in antibody production, and a diminution in the amount produced, in the test patients; this was associated with the reduction in number of circulatory lymphocytes. The author agrees with Bunting that microphages and macrophages play no part in the formation of antibodies, but by breaking down antigens into simpler substances prepare them for utilization by the lymphocytes. Exposure to *x* rays by inhibiting the lymphocytes would thus delay or prevent antibody response. Similar examinations of cases of Hodgkin's disease (3), chronic leukaemias (7 myeloid and 5 lymphatic), lymphosarcoma (5), and lymphofollicular reticuloses (2) revealed poor agglutinin responses except in myeloid leukaemias; these failures of antibody formation may be related to and proportional to the disorganization of the lymph nodes in these diseases.
John F. Wilkinson

2092. **The Influence on the Formation of Antitoxin Exercised by Dead Diphtheria Bacilli Added to Diphtheria Toxoid in the Immunization of Rabbits and Horses.** [In English]
A. LITHANDER. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 439–443, 1948. 12 refs.

As judged by experiments on a small number of rabbits and horses, the addition of 2% moist weight of formalin-killed diphtheria bacilli to diphtheria toxoid converted it into an antigen as good as diphtheria toxoid plus tapioca; the antigen so produced was less irritant and gave rise to fewer abscesses than did tapioca-treated toxoid. *C. L. Oakley*

2093. **Preparation of Purified Antitoxins.** [In English]
A. HANSEN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 460–484, 1948. 7 figs., 4 refs.

In the author's method for purification of antitoxins, 8 litres of blood from immunized horses are taken into acetate-lactate buffer (80% lactic acid 130 ml., sodium acetate 155 g., sodium hydroxide 52 g., sodium chloride 125 g., distilled water to 22 litres), the mixture acidified to *p*H 5·5 with hydrochloric acid (450 ml. N.HCl diluted to 500 ml. with distilled water) and " clotted " by addition of 1,280 ml. 2% " bentonite ". The fibrin coagulum and red cells are removed by centrifugation; the serum protein supernatant is cleared by further bentonite treatment, determined by experiment. The clarified protein solution is then adjusted to *p*H 3·2 with half-normal hydrochloric acid and digested with pepsin solution (final concentration 2 U.S.P. units per ml.) for 18 hours at 20° C., with readjustment of *p*H to 3·2 one hour after addition of pepsin. The digestion is interrupted by adjustment of *p*H to 6·5 by cautious addition of half-normal NaOH with vigorous stirring. Non-specific proteins are removed by adsorption on aluminium hydroxide gel, repeated up to five times till the material is clear, and the product is ultrafiltered through collodion membranes supported on porous porcelain kidney filters, and concentrated by addition of 290 g. ammonium sulphate per litre, filtration, and dialysis of the filter-cake against running tap water. *C. L. Oakley*

2094. **Behaviour of Heterogenous and Species-specific Alcoholic Organ Extracts in the Presence of Rabbit Serum with later Addition of Pig Serum.** (Über das Verhalten heterogenetischer und arteigener alkoholischer Organextrakte bei der Zwischenschaltung von Kaninchenserum und nachträglicher Zugabe von Schweineserum)
F. HEIMANN. *Schweizerische Zeitschrift für Pathologie und Bakteriologie* [*Schweiz. Z. Path. Bakt.*] **11**, 1–10, 1948. 11 refs.

The author shows that heterogenetic organ extracts (such as alcoholic extracts of horse kidney) and alchoholic rabbit organ extracts are not antigenic alone, and are made fully antigenic when treated with pig serum diluted with sodium oxalate and calcium chloride solution, but are not antigenic when treated with rabbit serum before treatment with pig serum. (Antigenicity tests were carried out in rabbits.) He therefore concludes that Landsteiner's view that the real antigen is an organ-extract–protein complex is unsound, and that the foreign protein merely coats the organ-extract molecules and carries them with it to the antibody-producing cells, while the autologous protein though it coats the organ-extract molecules in a similar way has no capacity to carry them to the antibody-producing cells.
C. L. Oakley

Paediatrics

2095. **Salicylate Tolerance and Toxicity in Children**
E. DUBOW and N. H. SOLOMON. *Pediatrics* [*Pediatrics*] 1, 495–504, April, 1948. 4 figs., 20 refs.

Salicylates in large doses (0·13 to 0·19 g. per kilo body weight daily) have recently been used in the treatment of rheumatic fever in young adults without evidence of toxicity, but conflicting reports have been published of the tolerance of children for comparable doses of the drug. Salicylate intoxication has been reported in children acutely ill with rheumatic fever, while equivalent dosage in convalescent children was well tolerated. After ingestion salicylate is rapidly absorbed, and although excretion by the kidney is also rapid, cumulative effects may result from prolonged 4-hourly administration. A decrease in carbon dioxide content of serum is found early, attributable to central stimulation of respiration rather than to acidosis; in fact there may at first be an alkalosis. A true acidosis develops later, with increased serum chlorides, loss of base in the urine, and accumulation of acid metabolites.

In this study a group of 19 children ranging in age from 8 months to 11½ years were treated with sodium salicylate or acetylsalicylic acid in doses of either 0·1, 0·125, or 0·15 g. per kilo body weight per day. The daily dose was given in four aliquot parts 4-hourly during the day; no alkali was given. Plasma salicylate levels, serum carbon dioxide content, and blood *p*H values were studied throughout. Six patients, from 3 to 11½ years old, were given 0·15 g. per kilo body weight daily. Five showed definite toxic symptoms—hyperpnoea, apathy and lassitude, anorexia, and tinnitus. Administration of the drug was stopped before more severe toxic symptoms occurred. Plasma salicylate levels in these cases ranged from 32 to 41 mg. per 100 ml. The one child who showed no toxic symptoms on this dosage was afebrile and convalescent when treatment started. Acetylsalicylic acid appeared to be more toxic than sodium salicylate. An early fall in serum carbon dioxide content, followed by a gradual further fall, was noted; blood *p*H rose at first, falling gradually later. The urine contained albumin, casts, red and white blood cells, and acetone. Gerhardt's test was positive constantly; reduction of Benedict's solution was noted occasionally. When the dose of salicylate was reduced to 0·1 g. per kilo body weight daily, plasma salicylate values averaged only 20 mg. per 100 ml., well below the advocated therapeutic level of 35 mg. per 100 ml. With the intermediate dose of 0·125 g. per kilo body weight daily, plasma salicylate values ranging from 30·9 to 39·4 mg. per 100 ml. were obtained. None of the children receiving this dose showed any symptom of toxicity after prolonged administration, and serum carbon dioxide content and blood *p*H values were normal. In infants and children under 3 years of age therapeutic plasma levels were not reached with doses of sodium salicylate up to 0·15 g. per kilo.

The early symptoms of salicylate toxication are hyperpnoea, anorexia, apathy, and lassitude. In the treatment of salicylate poisoning blood *p*H determinations give the best indication of the need for alkali therapy, for low serum carbon dioxide values may be due to centrally stimulated hyperpnoea and be accompanied by a rising *p*H. True acidosis with lowering of both carbon dioxide content and *p*H on the other hand is an indication for the free administration of alkali by oral and parenteral routes. Salicylate tolerance is diminished in acutely ill children, and here the dehydration of fever and vomiting, the accumulation of acid metabolites, and impairment of renal function dispose to intoxication. *P. T. Bray*

2096. **Oral Administration of Penicillin to Premature Infants and the Newborn.** (L'administration de la pénicilline par la voie buccale aux prématurés et nouveaunés)
R. GOSTOF and H. TROJANOVÁ. *Paediatria Danubiana* [*Paediat. danub.*] 3, 117–121, March, 1948. 3 figs., 9 refs.

In premature infants almost no difference was found between the effects of penicillin given by mouth or intramuscularly. A useful blood level was maintained for 6 hours after administration of 5,000 units. The drug was given in a spoonful of milk a quarter to half an hour before feeds; 4-hourly administration, however, was preferred in order to maintain a constant blood level. The same results were achieved in full-term infants with doses of 10,000 units. In infants over 1 month old penicillin should be given intramuscularly every 3 hours in doses of at least 5,000 units. *H. Herlinger*

2097. **Hunger Edema in Children**
E. P. PETRIDES. *Journal of Pediatrics* [*J. Pediat.*] **32**, 333–350, April, 1948. 14 figs., 17 refs.

Forty children out of a group of 106 with nutritional oedema in Athens were investigated to ascertain the relation between hunger oedema and the serum protein level, the value of animal protein in re-establishing normal protein levels, and the effect of this on the oedema. Most of the children were between 1 year and 3 years old; hunger oedema was not seen below the age of 6 months. Males were more often affected than females (6 to 4). The clinical picture was typical and the condition usually severe; 81 children out of the 106 recovered and 25 died (23·6%). The oedema disappeared by about the thirteenth day of treatment with gradual restitution of food intake.

The 40 children specially studied were divided into 4 groups. For the first, consisting of 30 children, the serum proteins were estimated refractometrically at intervals until recovery. The determinations showed continuously increasing levels and a parallel diminution

of oedema. In the second group there were 4 children and animal protein was withheld from the diet of 3 of them for periods varying up to 13 days. In these serum protein did not rise and in the younger children the oedema was increased. Animal protein (milk and eggs and cream) was then added to the diet, the caloric intake being kept stable by diminishing the fat and carbohydrate intake; the serum protein level immediately began to rise and the oedema disappeared when the level reached normal. The fourth child, aged 10, was given no animal protein, but a high vegetable protein diet and he reacted similarly. The author concludes that in older children vegetable protein can replace animal protein if given in sufficient quantity, whereas younger children need animal protein. In the third group of 3 children, 1 was given milk and sugar, the second egg-white and sugar, and the third egg-yolk and sugar. In the first and third there was a progressive increase in serum proteins and loss of oedema while in the second protein level remained consistently low (3·06 g.) and oedema did not improve. In the fourth group nutritional oedema was produced in 3 normal children by withholding animal protein. The serum proteins diminished steadily and oedema appeared after 39, 37, and 20 days respectively. All returned to normal when adequate animal protein was added to the diet. From these experiments the author concludes that nutritional oedema is due to hypoproteinaemia and that there is a direct relation between the two.

W. F. Gaisford

2098. **Normocalcaemic Tetany. Data Contributory to the Diagnosis of Idiopathic Tetany.** [In English]
F. GERLÓCZY. *Paediatria Danubiana* [*Paediat. danub.*] **3**, 134–150, March, 1948. 43 refs.

The different fractions of the total serum calcium and their significance are discussed. The potassium/calcium ratio (normally between 1·87 and 2·1) is an indicator of the level of the ionized calcium fraction and is of importance in the diagnosis of normocalcaemic tetany. If the ratio exceeds 2·1 tetany may occur with calcium values above 10 mg. per 100 ml., whereas if the quotient remains below 1·87 latent tetany will not be present even with very low calcium values. In tetany administration of " A.T.10 " results in clinical improvement and return to normal of the potassium/calcium quotient while the total blood calcium remains unchanged or may decrease. Three cases of normocalcaemic tetany are reported in detail.

H. Herlinger

2099. **Anaerobic Metabolism in the Newborn Infant. I. On the Resistance of the Fetus and Newborn to Oxygen Lack**
J. L. WILSON, H. S. REARDON, and M. MURAYAMA. *Pediatrics* [*Pediatrics*] **1**, 581–592, May, 1948. 5 figs., 17 refs.

The authors first discuss in detail investigations of others on the resistance of newborn animals to anoxia, as well as studies on the acid–base balance in normal full-term and premature infants. They record observations of the *p*H values and carbon dioxide content and tension in healthy premature infants, these determinations being carried out on temporal artery blood and capillary arterial blood plasma in 12 premature infants whose ages ranged from 3 to 45 days, and whose birth weights ranged from 1,120 g. to 2,000 g. The average *p*H value was found to be 7·3 with a range from 7·18 to 7·48. The average total carbon dioxide content in milliequivalents per litre was 19·3, with values of 12·7 and 25·3 as lower and upper limits respectively. From these results, which substantially confirm those of Raiha and Branning, the authors conclude that in premature infants there is an acidosis with a low *p*H, low total carbon dioxide content, and low carbon dioxide tension. This acidosis they presume to be due to an increase in blood organic acids, such as lactic and pyruvic acids.

Studying the effect of high oxygen concentration (70%) on the respiration of premature infants, they observed that the type of respiration occurring when the infants were in room air was periodic and this could be transformed to the normal form of breathing by administration of a high oxygen concentration. These observations indicate that in room air the total effectiveness of the pulmonary ventilation in premature infants is insufficient to prevent a type of respiration usually interpreted as resulting from oxygen lack. As it occurs in healthy premature infants the authors consider it to be evidence of the existence of a partial anaerobic type of metabolism which they plan to study further.

W. F. Gaisford

2100. **Growth and Physical Performance of Children in Relation to Maturity**
R. W. B. ELLIS. *Proceedings of the Royal Society of Medicine* [*Proc. R. Soc. Med.*] **41**, 343–348, June, 1948. 3 figs., 7 refs.

Assessment of growth and nutrition should take into account not only age but maturity, particularly in children over 9 years of age. In the present study 3 gradings were made—non-pubescent, pubescent, and adolescent—according to the presence or absence of breast development and of menstruation in girls and of pigmented pubic hair and genital development in boys. In 208 boys aged 11 to 16 years the development was observed, and it is remarked that the raising of the school-leaving age will affect the maturity of boys entering employment. It was found that boys who matured early were heavier and taller than those who matured late. Height and weight increase are accelerated just before pubescence. Physical performance in relation to maturity was also assessed.

Beryl Twyman

2101. **The Breast Feeding of Mature Infants during the Neonatal Period, and the Influence of Some Factors on the Same.** [In English]
J. STRÖM. *Acta Pædiatrica* [*Acta pædiatr., Stockh.*] **35**, Suppl. 1, 55–77, March 1, 1948. 7 figs.

The author's case material comprises 1,074 infants with a birth weight of over 2,500 g.; 43·9% of the mothers were primiparae and 56·1% were multiparae. A probable correlation both for primiparae and multiparae could be established between the infants' birth weights and the

total amount of breast milk secreted during the first 2 to 7 days. The latter was also found to stand in a negative correlation to the age of the mother. Only relatively serious illness of the mother was found to influence secretion of the mammary glands. Primiparae normally have a considerably smaller amount of breast milk at first, and all the factors that affect the latter adversely have a much greater influence in the case of the primiparae, but both in health or illness these differences between primiparae and multiparae rapidly disappear and are very small 1 week after delivery. [Good use is made of the statistical material.] *H. Herlinger*

2102. **Control of Air-borne Infections in a Nursery for Young Infants**

I. ROSENSTERN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **75**, 193–202, Feb., 1948. 5 figs., 7 refs.

An investigation into the methods of controlling air-borne cross-infection in a nursery for infants has been conducted over a period of 7 years. Air conditioning alone was ineffective, although when this was associated with germicidal irradiation of the upper air there was an improvement. Air conditioning with germicidal light barriers between beds was more efficient, as was air conditioning with mechanical barriers. The use of flannel and gauze face masks is recommended, although further investigations are being made to decide the most efficient forms. *N. M. Jacoby*

2103. **Encephalitis as a Causative Factor in Behavior Disorders of Children. An Analysis of Seventy-eight Cases**

J. V. GREENEBAUM and L. A. LURIE. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **136**, 923–930, April 3, 1948. 4 figs., 5 refs.

This is the third report by these authors, bringing the number of cases studied to 78 out of a total of 2,700 children referred for in-patient observation of behaviour problems. The follow-up period ranged from 4 to 26 years. The aetiology of the preceding encephalitis was a virus infection in 47·5%, a toxic condition in 37%, and trauma in 15·5%. In most cases the mental change was noticed immediately after the encephalitis, but strangely enough none of the cases was referred in the acute stage. Examination of the children revealed neurological signs in all but 21. The electroencephalograms of 15 children were normal in 6, abnormal in 8, and doubtful in 1. Behaviour changes were classified as: (1) simple behaviour disturbance (33%); (2) psychopathic behaviour (46%); (3) psychotic behaviour (21%). Intelligence tests on admission showed that 14 children were feebleminded, 7 were borderline, and 57 were of average intelligence or superior. In 47 cases the tests were repeated some years later, and it was found that in 9 the intelligence quotient was unchanged, in 1 it was improved, and in 37 it had deteriorated.

The authors consider that the prognosis is poor in spite of treatment; they give details of 3 cases.

N. M. Jacoby

2104. **Oxycephaly with Optic Atrophy. Report on Results of the King Operation**

J. V. LISMAN. *American Journal of Ophthalmology* [*Amer. J. Ophthal.*] **31**, 311–317, March, 1948. 8 figs., 12 refs.

Oxycephaly is a congenital abnormality of the bones of the skull in which there is premature synostosis of the face and head; increase of intracranial pressure and optic atrophy are common complications. Three groups are recognized. In the first there is closure of the sagittal suture and in the second the coronal sutures are involved, while in the third both are affected. The signs and symptoms are those of increased intracranial pressure. The size of the orbits may be decreased, and exophthalmos and lagophthalmos may be found. Vision usually becomes defective at an early stage. There is some doubt whether the optic atrophy is primary or secondary, but there appears to be little evidence that the optic foramen is small. A case is reported in which the right eye showed marked primary atrophy. This case was treated by the King morcellation operation. There was some immediate improvement of the vision in the right eye, but this was not maintained. It is pointed out that the optic atrophy may be due to the small size of the optic foramen, to papilloedema, or to distortion of the optic nerves by traction. The most rational treatment appears to be the linear craniectomy of Faber. Exophthalmos always recedes after operation. *A. G. Cross*

2105. **Congenital Megacolon. Results of Treatment by Spinal Anaesthesia**

E. D. TELFORD and H. A. HAXTON. *British Medical Journal* [*Brit. med. J.*] **1**, 827–828, May 1, 1948. 3 refs.

The late results in 12 cases of megacolon treated from 2 to 9 years previously are reported. Normal bowel action with improvement in growth, mental development, and complexion resulted in 8 of the cases. There was considerable improvement in another 2 patients, while treatment failed in the remaining 2 children. There may be a delay of several weeks after treatment before improvement is manifest. Good results are more certain in younger patients and 12 years seems the upper age limit for success. *H. Herlinger*

2106. **Stomatitis in Infants Caused by *B. mucosus capsulatus***

R. L. FAUCETT and H. C. MILLER. *Pediatrics* [*Pediatrics*] **1**, 458–461, April, 1948. 1 fig., 1 ref.

A type of membranous stomatitis observed in 6 infants (4 within the neonatal period) is described. In each case a Gram-negative organism probably belonging to the *Bacillus mucosus capsulatus* group was recovered from the lesions on culture; in 3 cases it was the only organism found and in the remaining 3 cases it was accompanied by *Monilia albicans*. The claim that the organism discovered was probably responsible for the disease is supported by: (1) the failure to find it in routine nose and throat cultures in the authors' paediatric service; (2) the fact that a specific antiserum made from the

first case agglutinated to a titre of 1 in 1,500 the organisms recovered from 2 of the remaining 5 infants; and (3) the uniform clinical features of the lesion and rapid response to treatment with sulphadiazine.

The lesions, which bore some resemblance to those of thrush, consisted of a dirty white membrane in patches, but with a tendency to become confluent. None of the patients showed evidence of systemic response, such as fever, vomiting, diarrhoea, or leucocytosis, but the mouth seemed painful, and one patient developed dehydration due to inadequate intake of fluids. The infection was resistant to 1% gentian violet, but responded quickly to sulphadiazine, gr. 1 (65 mg.) per pound (0·45 kg.) body weight per day. In one case cultures from the mouth became negative 4 days after the treatment was begun. Sulphadiazine was not so speedily effective when there was also monilial infection. Direct contact between the affected infants was not demonstrated. *N. B. Capon*

2107. **Infantile Cortical Hyperostoses.** [In English]
D. Van Zeben. *Acta Paediatrica* [*Acta paediatr., Stockh.*] **35**, 10–20, 1948. 9 figs., 4 refs.

Three cases of infantile cortical hypertostoses which presented features not hitherto noted are described. In all of them there were the characteristics found by Caffey —cortical thickenings in the bones and tender swellings deep in the soft tissues, though the peculiar facial expression caused by the latter in the region of the lower jaw, as described by Smyth, was not evident. In addition, a familial incidence was encountered (2 of the patients were siblings and the third was a cousin) and an anterior convex curvature of the thickened tibiae was seen radiologically. In each case the presenting symptom was swelling of the legs, associated in 2 cases with pain and impaired movement. Biopsy in one case revealed infiltration with osteoblasts, lymphocytes, and marrow cells. Culture and inoculation tests were negative. Two of the infants recovered; the third died of an intercurrent infection. *W. F. Gaisford*

2108. **Myasthenia Gravis in Young Children. Report of Three Cases—One Congenital**
J. R. Bowman. *Pediatrics* [*Pediatrics*] **1**, 472–477, April, 1948. 9 figs., 6 refs.

The author describes 3 cases of myasthenia gravis in children (ages $3\frac{7}{12}$, $6\frac{6}{12}$, and $8\frac{2}{12}$ years), and claims that one of them is the first recorded example of a patient with the symptoms and signs at birth. The other 2 children were cousins. Drooping of eyelids and of the corners of the mouth resulted in a sad expression—weakness of voice, fatigability on exertion, defective eye movements, and a tendency to respiratory symptoms were also noted. The mother of the infant with congenital myasthenia always had him photographed in the morning or following his afternoon nap " because his eyelids drooped less and his face showed more animation ". The author urges that the " prostigmin " test, in which 0·3 to 0·4 mg. prostigmin methylsulphate is injected intramuscularly, should be used for all children with ptosis of the eyelids; myasthenic signs disappear within 15 minutes. The paper includes a photomicrograph of atrophied muscle fibres removed from the anterior pillar of the fauces when a tonsillectomy was performed. The children improved remarkably under treatment with 30 mg. prostigmin (neostigmine, *B.P.*) bromide every 3 hours by mouth. *N. B. Capon*

2109. **The Electroencephalograms of Allergic Children**
S. C. Dees and H. Lowenbach. *Annals of Allergy* [*Ann. Allergy*] **6**, 99–108, March–April, 1948. 11 figs., 7 refs.

Electroencephalographic records were taken with a six-channel instrument, with unipolar and bipolar electrode systems, from 85 allergic children. The main feature was occipital dysrhythmia, which appeared in half the patients. There was correlation of this abnormality with a family history of allergy, with duration of personal history, and with youth. There was no correlation with the type or extent of the allergy. It is suggested that some psychic features of allergic disorders may be due to the disturbances in the central nervous system rather than to irritation due to symptoms.
W. Grey Walter

2110. **Receding Chin and Glossoptosis. A Cause of Respiratory Difficulty in the Infant**
A. Nisenson. *Journal of Pediatrics* [*J. Pediat.*] **32**, 397–403, April, 1948. 3 figs., 17 refs.

A commonly overlooked cause of cyanotic attacks in newborn infants is hypoplasia of the mandible. In this condition ptosis of the tongue causes mechanical obstruction of the larynx, cyanosis, dysphagia, and respiratory embarrassment. The infants may die of asphyxia or starvation, since the symptoms are aggravated during feeding. The literature on this subject is briefly reviewed and the findings are tabulated in 19 cases. A typical case is described in a 7-weeks-old infant. A special headgear was devised to push the chin forward; this the infant wore for a month and thereafter his progress was satisfactory. *Jas. M. Smellie*

2111. **Organic Acids and their Salts in the Treatment of Severe Rickets.** (Органические кислоты и их соли в лечении тяжелого рахита)
M. B. Kokhanova. Педиатрия [*Pediatriya*] No. 3, 13–14, May–June, 1948.

Nineteen children with severe rickets. and ranging in age from 1 year 4 months to 4 years, were divided into a control group of 8 and a " combined treatment " group of 11. The control group received 25,000 i.u. vitamin D daily for a month while the others received in addition 30 ml. of a 21% citric-acid solution and 15 ml. of a 26% solution of sodium citrate daily. Radiographs of the wrist regions were taken at intervals. In all but 2 of the group receiving combined treatment healing of bone took place more rapidly than in controls. In 5 cases a difference in the rates of deposition of calcium was obvious in radiographs after 2 weeks. *S. S. B. Gilder*

Medicine: General

ALLERGY

2112. **Action of a Synthetic Antihistamine Drug on the Blood Histamine Curve and on Certain Symptoms Due to Histamine in Asthmatic Patients.** (Azione di un antistaminico sintetico sulle curve istaminemiche e su alcuni sintomi prodotti dall'istamina negli asmatici)
U. SERAFINI and G. BIOZZI. *Policlinico, Sez. Pratica* [*Policlinico, sez. prat.*] **55**, 385–390, March 29, 1948.

Dimethylaminoethylbenzylaniline (" dimetina "; " antergan ") was given to 7 patients with asthma selected because histamine provoked in them an asthma of moderate degree. The level of histamine in the blood after subcutaneous injection of 1 mg. of histamine was studied in each patient by Code's method; it consistently showed a rise whose peak preceded the onset of asthma by a few minutes. Several days later a similar injection was given to the same patients one-half minute after intravenous antergan (2 ml. of 2%); the blood histamine level remained basal and none of the 7 had any difficulty in breathing. The authors remark that the uninhibited outpouring of histamine in the first experiment was quantitatively in excess of the 1 mg. injected, and suggest that it was due to a tissue reaction, presumably inhibited by antergan. Nevertheless, vasomotor reactions were not modified.

[Antihistamine drugs in asthma have been disappointing and the reasons for success and failure are being sought; it is a pity that the authors do not record the effect of the drug during an ordinary attack in their 7 patients. They neither describe their subjects nor state how coincidental therapeutic suggestion was avoided.]
John Hambling

2113. **Effects of Topical Applications of Diphenhydramine Hydrochloride (Benadryl)**
T. H. MCGAVACK, P. SCHULMAN, R. SCHUTZER, and H. ELIAS. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph., Chicago*] **57**, 308–318, March, 1948. 43 refs.

The authors noted that whilst diphenhydramine hydrochloride (" benadryl ") had a powerful antihistamine action, side-effects often occurred when the drug was taken by the mouth. They therefore decided to test its efficiency when used as a local application. Four different ointment bases were used and the benadryl was incorporated in strengths of 2 and 5%.

The cutaneous sensitivity to histamine of 63 individuals was determined by placing a drop of 0·1% solution of histamine diphosphate on the forearm and producing a wheal by causing minor trauma of the skin under the drop so that a small amount of histamine reached the dermis. The ointments were applied to the wheals thus produced, and the cessation of subjective symptoms and the subsidence of the wheals were observed. " Carbowax 1500 " monostearate was found to be the best base. Seventy-four patients with itching eruptions were treated with ointments containing benadryl; 59·5% obtained complete relief from the itching and 24·3% were partly relieved. Systemic effects did not occur. The optimum concentration of the benadryl appeared to be between 2 and 5%. *R. M. B. MacKenna*

2114. **Antihistaminic, Antianaphylactic and Antiallergic Activity of N-(α-Pyridyl)-N-(α-Thenyl)-N′, N′-Dimethylethylenediamine Hydrochloride**
A. S. FRIEDLAENDER and S. FRIEDLAENDER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 530–533, May, 1948. 5 refs.

The authors describe still another antihistaminic, antianaphylactic, and anti-allergic agent, " thenylene ", sometimes called " histadyl ". [There is nothing new in this paper beyond what has already been reported so many times about these agents, and the reader is referred to Abstract 558 in *Abstracts of World Medicine*, 1948, **4**, 163.] *G. F. Walker*

2115. **A Comparison of the Toxic Manifestations Produced by *beta*-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) and Tripelennamine (Pyribenzamine)**
T. H. MCGAVACK, J. WEISSBERG, and L. J. BOYD. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 595–601, May, 1948. 1 fig., 11 refs.

" Benadryl " and " pyribenzamine " were administered to a number of ambulatory patients except those suffering from acute illnesses, allergic conditions, or disturbances of the autonomic system. Altogether 80 women and 62 men, ranging in age from 18 to 80, completed the tests. Each drug was given for at least a week, and any given dose was maintained for not less than a week in any one case. To avoid drug tolerance neither drug was, as a rule, given in increasing doses. Of the 142 subjects, 52 received benadryl and 52 pyribenzamine alone, while the remaining 38 were given both drugs, the interval between the two courses being at least a fortnight.

The aim of the study was to determine the frequency of toxic reactions with each drug; all disturbances, however slight, were therefore recorded. With the usual therapeutic dose of 150 mg. a day, the incidence of reactions was the same with both drugs, that is, reactions were observed in 9 out of 14 cases. There were toxic reactions in 40 of the 52 patients given benadryl only in doses of 150, 300, 450, or 600 mg. a day, as compared with 35 out of 52 given the same amounts of pyribenzamine. With small doses of each drug signs and symptoms of toxicity were frequent but mild in degree, both drugs being well tolerated. Benadryl was more liable to

cause drowsiness and pyribenzamine dryness of the mouth; the latter tended to increase as the dose was increased. Tolerance to drowsiness usually developed in a few days with benadryl, except with the largest doses, when more severe cerebral disturbances were observed. Pyribenzamine was less likely to induce tolerance. Both drugs were given to 6 patients in doses of 150, 300, 450, and 600 mg. a day for 7 days or more at each level. With neither drug were there any toxic effects which persisted or became chronic after treatment was discontinued.

The authors conclude that, at the highest dosage, benadryl is the more toxic drug, and that at a dosage not exceeding 300 mg. a day both cause a large proportion of toxic reactions, which are not, however, serious enough for the treatment to be stopped. They point out that some of the effects of benadryl may be advantageous in treatment, as in itching skin conditions and in asthma. *Reginald St. A. Heathcote*

METABOLIC DISORDERS

2116. **Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone; Relation to Uric Acid Metabolism**
J. W. Conn, L. H. Louis, and C. E. Wheeler. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **33**, 651–661, June, 1948. 3 figs., 27 refs.

Two normal female 24-year-old students were given a constant diet (protein 99 g., carbohydrate 300 g., fat 176 g.) for 32 days. During the first 12 days a base-line was established, and during the next 8 days each subject received 120 mg. of adrenocorticotrophic hormone intramuscularly daily. A third male subject, 37 years old, also received a constant diet (protein 99 g., carbohydrate 300 g., fat 197 g.) for 33 days. After a 10-day base-line period he was given 150 mg. of hormone daily for 10 days. No immediate effects were experienced by any of the subjects, though 1 of the females developed itching and redness at the injection sites during the last 3 days of hormone administration. The male subject developed severe acne on the eighth day of injections. In both females gross irregularities of the menstrual cycle followed the injection period, but the next cycle was normal. In all subjects there was a four-fold to five-fold increase in the daily total excretion of 17-ketosteroids. A great retention of sodium and increased urinary excretion of potassium were also observed in all subjects.

The male subject showed the most striking disturbance of sugar metabolism. During the 10-day period of injections a total of 252 g. of glucose was excreted in the urine, and urinary content of nitrogen averaged 19·3 g. per day, compared with an average of 13·5 g. per day in the base-line period. The negative balance continued for 10 days after cessation of hormone injections. The glucose tolerance curves revealed a greatly decreased capacity to clear the blood of glucose under absorption, and this deficiency became apparent after 1 day of hormone administration.

The administration of hormone produced a large increase in uric acid excretion in urine, accompanied by a decrease in uric acid content of blood. It is thought possible that, during the increased production of uric acid, intermediaries, similar in their effects to alloxan, are produced and reach a critical intracellular concentration in the β cells. These intermediaries may diminish enzymatic production or release of pancreatic insulin. Studies on carbohydrate metabolism in the remaining 2 subjects gave similar results, though in 1 there was no loss of body protein. However, although greater loss of carbohydrate tolerance occurred in the 2 subjects with a marked negative nitrogen balance, the glycosuria was not related either in time or degree to the loss of body protein. There was a close correlation in all 3 subjects between loss of carbohydrate tolerance and increased uric acid excretion in urine. *R. B. Lucas*

2117. **The Course of Beriberi Heart Disease in American Prisoners-of-war in Japan**
R. J. Alleman and G. H. Stollerman. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 949–962, May, 1948. 3 figs., 26 refs.

It is generally thought that heart disease due to beriberi is accompanied by right heart enlargement and manifestations of a rapid circulation, and that a rapid response to aneurin (thiamin) therapy is diagnostic. More recently, the diagnosis has been made when there is evidence of gross dietetic deficiency together with peripheral neuritis in the presence of an enlarged failing heart for which there is no other explanation. Even failure to improve with aneurin does not exclude the diagnosis. Should the heart respond well to treatment with the specific vitamin relapses may still occur.

Two cases are described. In the first, there was a gross nutritional inadequacy, with widespread oedema, cramps in the legs, and incoordination. The patient improved on treatment with the ordinary cardiac remedies, which were given with aneurin, but very quickly relapsed. A further improvement occurred for a time, but in a third attack he died. Apart from some degeneration of the myocardial fibres and infiltration with small round cells, no other explanation of the failure was found at necropsy. In the second case the onset was similar, but the patient made a good recovery when given an adequate diet and large doses of vitamins orally and parenterally. The symptoms cleared up at the end of 4 months. *J. McMichael*

2118. **Observations on Pellagra in Early Infancy.** (Contribuição ao estudo da pelagra na primeira infância)
C. Pernetta. *Archivos Brasileiros de Medicina* [*Arch. brasil. Med.*] **38**, 97–151, April, May, and June, 1948. 15 figs., 39 refs.

The typical forms of infantile pellagra are frequently found among the poor of Rio de Janeiro. The very characteristic clinical picture consists of the classical triad seen in the adult—the gastro-intestinal, neurological, and cutaneous syndrome—together with oedema and inhibition of growth. An association with other specific deficiency conditions such as xerophthalmia, scurvy, or rickets is rare. Complicating infections,

the most severe being bronchopneumonia, are frequent. The course of the disease in infants is more acute than in adults, and the prognosis more serious. Death occurs, as a rule from secondary infection, mainly bronchopneumonia. Laboratory examinations reveal a constant reduction in blood protein, with a particularly low level of globulin. There is also a fall in calcium and phosphorus levels in serum. Whilst anaemia is a constant feature of the illness, the type varies; an orthochromatic anaemia is commonest, but in some cases the colour index is below or above unity. Fatty infiltration of the liver is a constant biopsy finding, and its degree corresponds to the gravity of the case. A fatty liver is invariably found at necropsy. The importance of a balanced diet in prophylaxis and treatment is obvious. Extracts of gastric mucosa have a remarkable curative action, and cause the fatty infiltration of the liver to disappear. The prognosis depends on the successful treatment of the complications. *Hilde Eisner*

2119. **The Relation of Thiamine Clearance to Blood Levels in Man**
M. C. BLANCHAER and E. CAMERON. *Journal of Nutrition* [*J. Nutrit.*] **35**, 391–397, March 10, 1948. 1 fig., 7 refs.

Both the level of thiamin in the blood and urinary clearance values have been proposed as indications of thiamin deficiency. The authors have examined 23 hospital patients with a view to determining the relation between the results given by the two methods, the red blood cells being used for determination of the blood thiamin levels. In the group of patients with a clearance of 90 μg. and less, a significant negative correlation was found between blood cellular thiamin and urinary clearance, which, it is suggested, may be related to a defective renal function. Low clearance values were found in the more severely debilitated patients and with increasing age. *O. L. V. de Wesselow*

2120. **Two Cases of Porphyria, Cutaneous and Abdominal, Treated with Folic Acid.** (Dos casos de porfiria, cutánea y abdominal, tratados con ácido fólico)
M. R. CASTEX, A. L. GARCIA, and J. F. ZELASCO. *Prensa Médica Argentina* [*Prensa méd. argent.*] **35**, 907–908, May 14, 1948.

Two cases of porphyria treated with folic acid are described. The first patient was a woman of 25 years who, for about 3 years, had complained of the appearance on the legs, arms, and hands of bullae, which would burst and leave pigmented scars. Her urine was found to be port-wine coloured; it also gave a strong red fluorescence with Wood's light and coproporphyrin was isolated in pathological amounts by Fisher's method. The authors gave the patient 20 mg. of folic acid daily for 10 days and instructed her to protect herself from the sun. After 1 month she was much better, and exposure to the sun did not produce fresh bullae. The quantities of porphyrins in the urine became normal. She remained healthy for 4 months. The second patient, a woman of 30, was admitted to hospital because of severe abdominal pain simulating cholecystitis. She was definitely jaundiced, but examination of the urine showed that it contained excessive amounts of coproporphyrin. She was treated with folic acid and improved considerably.

The authors wisely point out that porphyria is a disease characterized by remissions and hence the difficulty of assessing treatment; they do not understand how folic acid acts in these cases, but suggest a further trial in view of the apparent response. *Paul B. Woolley*

2121. **Idiopathic Familial Hyperlipemia Attended with Hepato-splenomegaly.** [In English]
E. HARSLÖF. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 140–155, March 31, 1948. 1 fig., 25 refs.

A case of idiopathic familial hyperlipaemia with hepatosplenomegaly in a boy of 16 is described. The symptoms were hyperlipaemia with considerable increase of the neutral fat and moderate increase of cholesterol and phospholipids, haemorrhagic diathesis, hepato-splenomegaly, dwarfism, and adiposogenital dystrophy. Skin manifestations of the eruptive papular xanthomatous type found in some of the 6 cases previously reported in the literature were absent. The patient's 2 brothers suffered from the same disease and died at the age of 28 and 8 years respectively. Evidence of xanthomatoses was also found in the boy's parents and in his 2 sisters. A low-fat diet reduced the hepato-splenomegaly and hyperlipaemia and a subsequent high-fat diet caused these symptoms to reappear. The aetiology of the disease is unknown. *E. F. McCarthy*

2122. **The Rôle of Hormones in the Treatment of Obesity**
M. M. KUNDE. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 971–988, May, 1948. 12 figs., 19 refs.

The author conducted a clinical experiment on obesity. Fifty patients suffering from obesity of various types were told not to heed their calorie intake and to dismiss all thoughts of endocrine disorder from their minds. All were instructed to eat anything they liked within the scope of a high-protein, low-fat, and low-carbohydrate diet. The fat was removed from the meat with scrupulous care and considerable reliance was placed upon eggs, creamless cheese, gelatin, vegetables, fish, and fowl. No other treatment was given, except for supplementary vitamins and minerals. The results were strikingly successful according to the charts and photographs reproduced, and the author records that the high-protein diet was associated with a reduction in blood pressure in patients with previous hypertension.

One of the deductions from the charts is that thyroid is of limited value in the treatment of obesity, and the author makes the sweeping statement that no hormones or gland products known to therapeutics are necessary adjuncts in the treatment of any type of obesity, except that associated with hypothyroidism. [The article contains some very striking photographs, and the clinical observations are given in the utmost detail, but some of the photographs of patients after treatment are missing; their presence would add to the value of the article.] *G. F. Walker*

Cardiovascular Disorders

HEART

2123. **Vitamin B_1 in Patients with Cardiovascular Insufficiency.** (Витамин $Б_1$ у больных с недостаточностью сердечно-сосудистой системы)
G. P. BOGDANOVA-BURGMAN. Клиническая Медицина [*Klin. Med., Mosk.*] **26**, No. 4, 75–81, 1948. 3 figs., 5 refs.

The daily urinary excretion of vitamin B_1 (aneurin) in patients with cardiovascular decompensation of grade II was significantly diminished in comparison with the normal (4 cases; 4 controls). Excretion was even less in 3 patients with grade III decompensation. In all groups the amount of vitamin B_1 excreted varied in relation to meals, rising after a meal and then falling again. After saturation with a vitamin B_1 preparation, there was a marked retention of the latter in patients with cardiac decompensation, the degree of retention being proportional to the degree of decompensation.

S. S. B. Gilder

2124. **The Mechanical Heart.** (Het mechanische hart)
J. JONGBLOED. *Nederlandsch Tijdschrift voor Geneeskunde* [*Ned. Tijdschr. Geneesk.*] **92**, 1065–1072, April 10, 1948. 2 refs.

The apparatus described was constructed and tested on dogs in the physiological laboratory of Utrecht University. It consists of an intermittent pump, with two compartments corresponding to the right and left heart, and an oxygenator composed of two co-axial cylinders. In all the experiments the animals were under an anaesthetic. The depth and frequency of respiration were observed, and the cardiac function was studied by means of electrocardiograms. In the preliminary experiments the thorax was laid open in order to study directly the behaviour of its contents. By means of T-cannulae inserted in the temporarily occluded venae cavae the blood was aspirated into the right compartment of the pump and led into the oxygenator, where—between the walls of its cylinders—it met a current of oxygen and 5% carbon dioxide. Thence it proceeded to the left compartment, from which it was driven into the aorta, also through a T-cannula. Thus the heart and the lungs were by-passed; the coronary vessels continued to receive their blood supply from the aorta. Artificial respiration was only necessary at the beginning of the experiment; later breathing became spontaneous, its frequency being regulated through the respiratory centre by the amount of CO_2 in the blood. When pure oxygen was supplied to the oxygenator the respiration stopped, to resume as soon as carbon dioxide reached the appropriate level in the blood. The heart, although empty, continued to beat regularly. It was easy to re-establish the organic circulation by ceasing to occlude the venae cavae and by stopping the pump. The reversal of circulation was made several times without affecting the vital functions.

In the second series of experiments the blood was aspirated from the venae cavae by means of catheters introduced through the right jugular vein and one of the femoral veins; after passing through the artificial heart it was pumped back into the body through T-cannulae inserted into the common carotid artery and one of the femoral arteries. In further experiments the entry through the carotid was abandoned and both femoral arteries were used instead. Evidence is quoted that no blood, or very little of it, passed through the heart or lungs; pulsation in the peripheral arteries followed the rhythm of the pump. There were no abnormal macroscopical changes in animals killed after the experiments. By stopping the pump the normal circulation was immediately re-established.

The author is still improving his apparatus and is building one to be used for operations on the human heart. There are still certain difficulties to overcome. For example, for the proper functioning of the mechanical heart an anticoagulant is needed, the presence of which might be detrimental in the event of operation. Nevertheless, the simplicity and reliability of the apparatus augur well for its practical application in the near future.

A. Lilker

2125. **Endocardiac Potentials in Right Heart Hypertrophy. Comparison with the Oesophageal Electrocardiogram.** (Potenciais intracavitários na hipertrofia ventricular direita. Sua comparação com o eletrocardiograma esofageano)
P. SCHLESINGER, A. BURLAMAQUI ENCHIMOL, and M. R. COTRIM. *Arquivos de Clínica* [*Arch. Clin.*] **6**, 139–155, March, 1948. 10 figs., 10 refs.

Endocardiac electrocardiograms are of recent origin, the first ones having been obtained in dogs and later ones in human subjects by means of cardiac catheterization. Sodi has recently compared the findings in the dog and in human subjects and Battro and Bidoggia have drawn attention to the similarity of the ventricular complex with the electrode in the right auricle and with the oesophageal lead in both healthy and diseased individuals. This paper deals with 5 cases of right-sided hypertrophy. The electrode, attached to a fine insulated wire, is introduced through the right external jugular vein, " sodium amytal " being used as premedication. There were no untoward effects, penicillin being given subsequently for 48 hours. Standard, unipolar, and precordial leads, and leads with the electrode at different intra-auricular and intra-ventricular levels were taken. The P wave is negative with the electrode at a high auricular level and gradually becomes positive as the electrode passes into the ventricle; the QRS complex at auricular level

was positive in 3 cases and negative in 2. The ST segment was elevated in 3 cases when the electrode was in the ventricle. The oesophageal leads, taken at auricular level, were found to have QRS complexes similar to those taken at intra-auricular level. Very similar complexes were also found with the unipolar VR lead. Some anomalous changes were thought to be due to the impulse passing over the wall of the interventricular septum.

Paul B. Woolley

2126. **The Arterial Oxygen Saturation in Cyanotic Types of Congenital Heart Disease**

G. E. MONTGOMERY, J. E. GERACI, R. L. PARKER, and E. H. WOOD. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **23**, 169–176, April 14, 1948. 2 figs., 8 refs.

This communication deals with the application of the oximeter to measurements of oxygen saturation of the blood. The oximeter used was that described by Millikan in 1942 and fitted with a photo-electric colorimeter. The oxygen saturation of the blood is measured directly by fitting the apparatus on to the human ear. The first study was concerned with the oxygen saturation of the blood in 25 patients with lesions belonging to the cyanotic group of congenital cardiac defect, such as the tetralogy of Fallot, the Eisenmenger complex, cor triloculare, and interventricular and interauricular septal defects with right-to-left shunt; 19 healthy subjects served as controls. Readings of oxygen saturation of arterial blood were taken and the effects of breathing 100% oxygen, change of posture, and exercise were particularly noted. The results are given in the table below.

		Increase in Arterial Saturation Breathing 100% O_2 (percentage points)	Time to Reach Maximal Increase (minutes)	Effect of Standing Posture (percentage points)	Effect of Walking 1·7 Miles per Hr. (percentage points)	Time from Start of Walk to Maximal Change (minutes)
25 Patients	Mean	6·2	3·2	−2·2	−11·2	3·5
	Range	2·0 to 16·5	0·5 to 5·0	−10·0 to +3·0	−3·5 to −19·0	1·0 to 5·0
19 Normal Controls	Mean	2·7	1·3	0·0	−0·3	—
	Range	1·0 to 5·0	0·5 to 3·0	−1·0 to 0·0	−2·0 to 0·0	— —

Interesting data are given on one patient with the tetralogy of Fallot, who, when exercised on the treadmill for 5 minutes at 1·7 miles per hour, showed a fall of arterial oxygen saturation from 80 to about 50%; in a normal subject in the same circumstances the oxygen saturation increased slightly.

The second part of the paper deals with the determination of arterial oxygen saturation at rest and during exercise in 8 cyanotic patients. This was done both by the Van Slyke method and by oximeter readings. The results were then compared and it was found that the average decrease in saturation on exercise was 19·5% by the Van Slyke method, while the simultaneous oximeter readings indicated a 13·3% decrease. Thus the discrepancies are large, but, as the authors say, " the instrument is still of considerable value in estimating the degree of disability of a patient and in judging the efficacy of corrective surgical procedures in such patients ". Suitable data are given in support of these statements.

A. I. Suchett-Kaye

2127. **The Changes in the Electrocardiogram Associated with Standing**

D. SCHERF and M. SCHLACHMAN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 150–153, May, 1948. 4 figs., 13 refs.

The changes in the electrocardiogram associated with standing were investigated in 80 male patients without evidence of organic heart disease. Records were taken with the patients in the supine position, after standing for 1 minute, 5 minutes and 15 minutes, and again immediately upon resuming the supine position. In order to investigate the part played by the tone of the sympathetic nervous system 0·5 mg. of dihydroergotamine (" DHE 45 ") was given intravenously to 12 patients and records were again taken in the supine and erect positions when the drug effect was at its height. In 25 patients (31·2%) there were significant changes in the electrocardiogram on standing, but neither the kind nor the time of appearance of changes was uniform. In 4 cases temporary A-V rhythm was observed as a result of change of posture. In 11 out of 12 cases changes occurring immediately on standing could not be prevented by dihydroergotamine. It is concluded that the immediate and delayed changes in the electrocardiogram must be ascribed to different mechanisms. The former are due to the change of position of the heart and altered contact between the heart and neighbouring structures, the latter to changes in the tone of the sympathetic nervous system acting on the heart either directly or through the coronary arteries.

A. Schott

2128. **Clinical Value of Unipolar Chest and Limb Leads**

C. W. C. BAIN and E. MCV. REDFERN. *British Heart Journal* [*Brit. Heart J.*] **10**, 9–25, Jan., 1948. 19 figs., 14 refs.

With the unipolar method of Wilson, a series of 300 twelve-lead electrocardiograms have been taken and analysed. This technique permits more accurate diagnosis of left ventricular hypertrophy; this was diagnosed in 90% of the cases in which it was considered to be present on other grounds. Left axis deviation was present in only half of these cases. Although these leads were not so reliable for the diagnosis of right ventricular hypertrophy, it was found possible to recognize hypertrophy of both ventricles from a combination of signs of left ventricular hypertrophy in the chest leads and a vertical heart. It was almost always possible to determine the side of the lesions in bundle-branch block, and by this method antero-septal and

antero-lateral types of myocardial infarction could be distinguished. It is considered that while this will become the standard method of taking chest leads because of its accuracy, the technique is not practical for general use on account of the time required to take a twelve-lead electrocardiogram. On the other hand, three chest leads give a reasonably accurate picture if they are varied according to circumstances.

[This important article should be read in the original by all who are interested in cardiovascular disease. It is the most comprehensive study yet published in Britain. Twelve-lead electrocardiograms will clearly become of increasing importance in cardiological practice, but there will be general agreement with the authors' warning that " it seems certain that it must be a long time before the knowledge which has been accumulated regarding the standard leads can be safely discarded ".]

William A. R. Thomson

2129. **Cardiovascular Changes Following Electro-convulsive Therapy**

R. KAUNTZE and G. PARSONS-SMITH. *British Heart Journal* [*Brit. Heart J.*] **10**, 57–62, Jan., 1948. 4 figs., 12 refs.

This is a study of 51 patients (38 women and 13 men), aged 24 to 69 years, in 82% of whom the presenting psychiatric symptom was depression. The Strauss and MacPhail convulsant apparatus was used, and the usual dosage was 18 joules diphasic. Electrocardiograms and blood pressure readings were taken before the convulsions and in the recovery phase directly after the clonic movements had ceased. Observations were made before and after 63 convulsions. The pulse rate increased in 56 instances after the convulsion, decreased in 3 instances, and remained unchanged in 4. The systolic blood pressure was raised in 19 instances, decreased in 21, and remained unchanged in 23. The increase ranged from 20 to 35 mm. Hg, and in a number of cases was accompanied by a small fall in the diastolic pressure. The maximum rise was from 135/70 to 190/95 in a man aged 27, while the maximum fall was from 135/100 to 120/80. Unfortunately, no details are given of the results in the 15 hypertensive patients in the series, except that the 3 with " severe hypertension " showed slight elevation of the systolic or diastolic pressures, or of both. As the post-convulsive blood-pressure readings were taken after the second electrocardiogram, there was some delay between the end of the fit and the recording of the pressure; it is therefore pointed out that the pressure may actually have been higher during the convulsion. Preliminary observations in patients who had curare and " pentothal " showed a small initial fall and then following the convulsion there might be no considerable rise in blood pressure. The main electrocardiographic changes after convulsions were: increase in the height of P_2, prolongation of the P–R interval, increase in the amplitude of T_2, T_3, diminution of R_1, and depression of $S–T_2$. The prolongation of the P–R interval ranged from 0·02 to 0·06 second and occurred in 52% of cases. Only 4 patients showed heterotopic beats after the convulsion, and these consisted of auricular, nodal, and ventricular premature beats. It is suggested that the changes in P_2, T_2, R_1, and $S–T_2$ are the result of " muscular activity " and that the delay in A–V conduction time is due to anoxia. The practical conclusion is that in middle-aged and elderly patients electrocardiograms should be taken before electroplexy, and that " although evidence of coronary disease is a strong contraindication, on occasion psychiatric considerations may be so imperative as to override this ".

William A. R. Thomson

2130. **Adreno-sympathogenic Heart Disease (Neurohormonal Factors in Pathogenesis and Treatment)**

W. RAAB. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 1010–1039, May, 1948. 15 figs., bibliography.

The author points out that mechanical overload is not necessarily the whole explanation of hypertensive heart disease. Many of the features of hypertensive heart disease may be found without hypertension. He calls attention to the possible pathogenic role of adrenaline and allied substances. Adrenaline intensifies the oxygen consumption of the heart, and may induce a state of anoxia. The metabolic changes induced by the drug in the heart are identical with those found after experimental anoxia in diseased human hearts and in animal hearts after severe exercise. The author considers that anginal attacks are accompanied by abnormal elevation of the adrenaline-sympathin levels in the blood. Hypertensive heart disease is not necessarily accompanied by any rise in adrenaline level in the blood, but abnormally high elevations of the levels of this and similar substances may follow physical exercise in patients with hypertension. The electrocardiographic features of hypertensive heart disease are similar to those which result from the injection of adrenaline, and it is emphasized that the abnormal electrocardiogram may revert to normal after sympathectomy, even if the patient remains hypertensive. The author develops similar arguments to account for changes in the heart in uraemia, thyrotoxicosis, and beriberi. These arguments are supported by a very extensive bibliography of 235 references. *J. McMichael*

2131. **Prolonged Paroxysmal Auricular Tachycardia. Report of a Case Including Treatment with Veratrum Viride**

E. W. SHAW. *New England Journal of Medicine* [*New Engl. J. Med.*] **238**, 654–656, May 6, 1948. 2 figs., 20 refs.

A boy aged 5, who had previously been healthy, developed diphtheria on Feb. 4, 1947; he was treated promptly with antitoxin and penicillin. On March 18 he developed chickenpox and on April 11 moderately severe measles. On April 3 he started paroxysmal auricular tachycardia at a rate of 140, with inverted P waves in all limb leads. The tachycardia still persisted at the time the author recorded his observations (October) without signs of failure or other cardiac impairment. Treatment with quinidine, " digitoxin ", and " mecholyl " did not interrupt the tachycardia for more than a few minutes at a time and eventually proved ineffective. A

preparation of veratrum viride by mouth converted the paroxysmal tachycardia into sinus rhythm with normal P waves for 15 hours at the first attempt and for shorter periods on two subsequent occasions. Thereafter it also had no effect. *G. Schoenewald*

2132. **Course and Treatment of Ventricular Paroxysmal Tachycardia.** (Sobre evolución y tratamiento de las taquicardias paroxísticas ventriculares)
F. C. ARRILLAGA and L. DE SOLDATI. *Medicina* [*Medicina, B. Aires*] **8**, 1–15, Feb., 1948. 4 figs., 23 refs.

The authors provide further evidence of the effectiveness of quinidine administered intravenously in the treatment of paroxysmal ventricular tachycardia. They report six attacks, varying in duration from 3 to 21 days, in 4 patients (aged 38 to 50 years) with no previous evidence of heart disease. Although only 1 of the patients developed signs of permanent heart disease, the authors call attention to the grave prognosis that usually accompanies these attacks. *W. T. Cooke*

2133. **Ball Thrombus of the Heart**
M. E. EVANS. *British Heart Journal* [*Brit. Heart J.*] **10**, 34–38, Jan., 1948. 3 figs., 18 refs.

The patient in the case reported here was a woman, aged 50, who suffered from mitral stenosis and multiple embolic phenomena, and who died from uraemia. Necropsy revealed thrombi in both kidneys, superior mesenteric artery, spleen, and both legs. A free ball thrombus was found in the left auricle, The literature is reviewed. *G. Schoenewald*

2134. **Mass Thrombus of the Left Auricle**
W. EVANS and R. BENSON. *British Heart Journal* [*Brit. Heart J.*] **10**, 39–47, Jan., 1948. 2 figs., bibliography.

Six cases of mitral stenosis are reported in which large thrombi, attached and free, were found in the left auricle. The use of the term " mass thrombus " for attached and unattached thrombi is advocated. The symptoms and signs in these 6 cases and in others taken from the literature are compared with those seen in cases of cardiac tumours. No single symptom or sign was found to be pathognomonic for a mass thrombus, but the typical anginal pain occurring either spontaneously or on effort in 3 of the 6 cases is considered a significant pointer to the diagnosis, especially in view of the comparative rarity of angina in mitral stenosis in general and in auricular fibrillation (present in the authors' 3 relevant cases) in particular. *G. Schoenewald*

2135. **Calcareous Aortic Stenosis and Coronary Artery Disease**
M. J. HORAN and A. R. BARNES. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 451–455, April, 1948. 15 refs.

In order to determine the degree of coronary sclerosis in calcareous aortic stenosis 100 cases selected to give a representative number of cases in each age group were studied and the clinical and post-mortem findings analysed. [It is not clear what is meant by " representative number " nor whether diagnosis was primarily clinical or based on the post-mortem findings.] Three patients were under 40 years of age, 12 in the fifth decade, 24 in the sixth, 19 in the seventh, 31 in the eighth, and 11 in the ninth. The degrees of stenosis at the aortic orifice and in the coronary vessels were assessed in percentages, less than 25% occlusion being grade 1, 25 to 49% grade 2, 50 to 74% grade 3, and above 75% grade 4. [It is not clear how 74% stenosis was assessed.] In 69 cases there was dyspnoea, in 28 angina, in 26 orthopnoea, and in 12 dizziness. There was a harsh loud basal systolic murmur in 60 cases [no mention being made of a thrill], cardiac enlargement in 53, and of 52 cases in which electrocardiography was performed left ventricular strain in 15 and left axis deviation in 12. It is stated that there seemed from necropsy observations to be a tendency for the degree of coronary sclerosis to be inversely proportional to the degree of aortic sclerosis. [The figures given do not clarify this point.] Only 2 of 7 patients with 25 to 75% obliteration of the coronary arteries had a history of angina. Twenty-nine patients had hypertension, usually of the " essential " type, and 20 had old or recent myocardial infarction; 42 died from cardiac disease, 18 suddenly with 6 deaths from pulmonary embolism. Although only 19 patients gave a history of rheumatic fever, calcareous aortic stenosis is regarded as a consequence of rheumatic fever. It is a relatively mild disease compared with mitral stenosis, as the low incidence of death from cardiac disease in this series indicates. No conclusion is drawn about its relation to angina pectoris, but the inconstant relation of aortic and coronary lesions to anginal symptoms in the series indicates that, besides coronary sclerosis, age, pain threshold, intercurrent disease, and myocardial lesions must be taken into account.

[The uncertain method of selection of cases and assessment of lesions make the conclusions on the point primarily investigated doubtful and disappointing.]
W. A. Bourne

2136. **The Variation of Casual, Basal, and Supplemental Blood Pressures in Health and in Essential Hypertension**
J. A. KILPATRICK. *British Heart Journal* [*Brit. Heart J.*] **10**, 48–56, Jan., 1948. 13 figs., 10 refs.

Casual blood pressure (meaning blood pressure as determined under ordinary clinical conditions), basal blood pressure (that is, blood pressure as estimated under conditions similar to those obtaining in determination of basal metabolism), and supplemental blood pressure (meaning the difference between casual and basal blood pressure) were recorded repeatedly in three groups of patients—those with normal blood pressures, prehypertensive patients, and patients with essential hypertension. Casual blood pressure showed the greatest fluctuations in the hypertensive group and the smallest fluctuations in the normal group. The fluctuations in the diastolic pressures of all three groups were hardly less than the fluctuations in the systolic pressures. Basal blood pressure in the normal subjects was found to be

almost a constant value; it showed minor fluctuations in the pre-hypertensive group and gross fluctuations in the hypertensive patients.

In a further investigation the patients with hypertension were sub-divided into those with compensated and those with failing hearts, and the supplemental blood pressures were determined. As was expected from the previous investigation, mean supplemental pressure was lowest in the normal subjects, higher in the pre-hypertensive patients, and highest in the hypertensive patients without failure. The 12 hypertensive subjects with heart failure had the lowest mean supplemental pressure of all groups—namely, 9 mm. of mercury compared with 18·2 mm. in the normal subjects, 25·0 mm. in the pre-hypertensive patients, and 44·6 mm. in the hypertensive patients with compensation. The possible causes of the rigidity of blood pressure values in the hypertensive patients with failing hearts are discussed.

G. Schoenewald

2137. **A New Conception of Angina Pectoris**
R. WYBURN-MASON. *British Medical Journal* [*Brit. med. J.*] **1**, 972–975, May 22, 1948. 33 refs.

From a review of the literature, and without any additional data apart from 2 case records, the hypothesis is advanced that " in all cardiac conditions in which angina or coronary pain is experienced there is evidence of excessive activity in the vasodilator pain fibres passing to the coronary vessels, and this is evidently the origin of the anginal pain ". To explain the close correlation between coronary sclerosis and angina pectoris it is suggested that the prevention of vasodilatation by coronary sclerosis permits of the accumulation of metabolites, and that these cause " excessive numbers of reflex impulses in the coronary vasodilator pain fibres in an attempt to produce further vasodilatation, and it is this excessive nervous activity which appears to give rise to the pain in such conditions ".

[This is a useful, if not particularly comprehensive or critical, review of the subject and should be read in the original. As a piece of " special pleading " it is quite effective, but the issues are not so simple as the author would appear to suggest. That cardiac pain can be induced reflexly all will admit, but the number of cases in which this occurs is small compared with that vast majority in which the pain is associated with coronary disease. It is significant that no reference is made to the universal use of the nitrites in alleviating the pain, and that the work of the Canadian investigators (Hall and his colleagues) on the effect of vagal stimulation is ignored.] *William A. R. Thomson*

2138. ***X*-Ray Therapy in the Treatment of Coronary Pain.** (Efectos de la radioterapia en el tratamiento del dolor coronario)
L. PESCADOR and A. MARTIN DE PRADOS. *Medicina Española* [*Med. esp.*] **19**, 235–240, March, 1948. 2 refs.

The authors treated 27 patients suffering from angina pectoris. The factors were 180 kV, 4 mA; filters, 1 mm. copper and 1 mm. aluminium; skin-focus distance 40 cm. The area was about 150 cm.^{2} between the inferior border of the clavicle and the mandibular angle, the patient's head being turned to the right. Thus, the irradiation was directed at the stellate ganglion, the periaortic plexus, and part of the sympathetic chain. It was carried out in five sessions at various intervals. [Length of sessions not stated.]

In 5 cases the results are not known. In 2 cases the pain was increased and the minimum blood pressure raised. In 2 other cases there was no change. In the remaining 18 cases the pain either disappeared altogether or its intensity and length were reduced, while the diastolic blood pressure decreased. *A. Lilker*

2139. **Perforation of the Infarcted Interventricular Septum. Report of Two Cases, one Diagnosed Antemortem**
N. O. FOWLER and R. B. FAILEY. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 534–541, May, 1948. 6 figs., 17 refs.

Two cases of perforation of the infarcted interventricular septum are reported. In one of them the diagnosis was made during life. A review of the literature revealed 56 similar cases, in 15 of which the diagnosis was made during life. The condition should be suspected in any patient who, shortly after a myocardial infarction, suddenly develops a systolic thrill and murmur in the third and fourth intercostal spaces just to the left of the sternum. These patients tend to develop right ventricular failure. In 38 cases the survival time was described, this being less than a month in 31. A further 6 patients died within a year, and 1 patient lived 4 years and 10 months. Out of 45 patients examined 43 had a systolic murmur, which in 22 was associated with a thrill. Rupture of a papillary muscle following infarction may be confused with this condition, but in the former the murmur tends to be heard best nearer to the apex, the patient's condition deteriorates rapidly, and the heart failure is left-sided rather than right-sided.

C. Bruce Perry

2140. **Angina in Women**
V. K. SUMMERS. *British Heart Journal* [*Brit. Heart J.*] **10**, 4–8, Jan., 1948. Bibliography.

The findings in a series of 87 cases of angina pectoris occurring in women are analysed. The age distribution showed that the majority of patients (54) were in the age group 40 to 60, only 3 patients being under 40. An interesting feature is that 12 patients were over the age of 70. No close association between either parity or the menopause and the incidence of angina was noted. Defining hypertension as a systolic pressure above 150 mm. Hg or a diastolic pressure above 90 mm. Hg, the author found an incidence of hypertension of 84%. A definite history of myocardial infarction was obtained in 34 patients; a less definite history in another 14. There was electrocardiographic evidence of coronary disease in 57 cases. The highest incidence of coronary disease (83%) occurred in the sixth and seventh decades. Only 1 patient had a syphilitic aortic incompetence, and there was no case of mitral stenosis. Two patients

had myxoedema, but both had hypertension. There was no case of hyperthyroidism. All 4 patients in the series with diabetes mellitus had hypertension. Six patients had anaemia; 2 of them were under the age of 40 and in them the anginal symptoms disappeared when the anaemia was relieved. Only 13 of the patients were classified as obese; 17 of the patients smoked, but there was no definite correlation between the smoking and the angina. The incidence of gall-bladder disease was low: 2 patients had gallstones and 3 gave a history suggestive of chronic cholecystitis.

[This is an interesting study in view of the relative infrequency of angina pectoris in women as compared with men. It confirms the generally accepted belief that the underlying pathology is the same in the two sexes—that is, coronary-artery disease.]

William A. R. Thomson

2141. **Experiences with a New Synthetic Analgesic, Amidone: Its Action on Ischemic Pains of Occlusive Arterial Diseases**

R. J. POPKIN. *American Heart Journal* [*Amer. Heart J.*] **35**, 793–799, May, 1948. 6 refs.

" Amidone " (methadon, " physeptone ") (6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride), which resembles morphine in its action, was given to a number of patients with peripheral vascular disease who suffered from pain at rest. The dose was 5 to 15 mg. by mouth. The drug relieved the pain at rest but was ineffective in intermittent claudication. One of the 18 patients developed a haemorrhagic urticaria and ambulant patients suffered from light-headedness, nausea, and vomiting. *H. E. Holling*

2142. **Experience with the Schemm Regimen in the Treatment of Congestive Heart Failure**

A. A. NEWMAN and H. J. STEWART. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 916–939, May, 1948. 9 figs., 14 refs.

The importance of a low salt intake in controlling oedema is now widely recognized. It has even been shown that, provided the salt intake is low, large amounts of fluid may be taken without increasing cardiac oedema. Schemm carried this principle to the point of recommending a very high daily fluid intake with a diet low in sodium and yielding a neutral or acid ash residue. Thirty patients were admitted to hospital for trial of this regime. Failure to maintain a steady state of oedema during a control period led to the elimination of 21 patients from later analysis. In only 9 were the data satisfactory. The regime alone was without beneficial action. Five of the patients were quite unable to consume the large amounts of water recommended. Moreover, the diet was not liked by the majority of patients. After an adequate trial of the Schemm treatment, the condition in 7 patients was found to be much improved on a regime of restricted salt, limited fluid and frequent administration of mercurial diuretics. Analysing critically the charts in Schemm's papers, the authors do not think that diuresis was achieved on his regime. The only occasions on which the patients lost weight were when mercurials were given. *J. McMichael*

DISORDERS OF CIRCULATION

2143. **Papaverine in Cerebral Angiospasm (Vascular Encephalopathy)**

H. I. RUSSEK and B. L. ZOHMAN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **136**, 930–392, April 3, 1948. 3 refs.

Papaverine relaxes the smooth muscles of the blood vessels. It has not previously been used for disturbances of the cerebral circulation, such as embolism and the angiospastic phenomena seen in various types of hypertensive disease. In the authors' opinion the transient character of these seizures suggests that spasm of the vessels is an important causal factor. Four cases are described in which attacks became less frequent or ceased when papaverine hydrochloride was given by mouth. One of the patients had recurrent attacks of weakness on the left side, coming on 5 to 20 times a day; blood pressure was normal and improvement followed administration of papaverine. The dose of the drug ranged from gr. 4 to 18 (0·26 to 1·2 g.) a day by mouth. The toxicity is low, and the drug has no narcotic action. It is thought that vascular encephalopathy is a more appropriate designation than hypertensive encephalopathy, since hypertension is absent in some cases. The authors also obtained encouraging results in cases of hypertensive headache.

[The occurrence of transient focal cerebral symptoms without evidence of vascular disease is difficult to account for. In one case described, evidence of an organic basis was lacking. Such attacks are more likely to be hysterical. Most of the transient attacks in hypertension are, in fact, due to small thromboses.] *J. McMichael*

2144. **Effect of Continued Desoxycorticosterone Administration in Hypertensive Subjects**

G. A. PERERA. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 48–50, May, 1948. 1 fig., 5 refs.

The effect upon blood pressure, serum electrolytes, and fluid balance of the subcutaneous administration of desoxycorticosterone (DOCA) over prolonged periods was investigated in 5 patients suffering from uncomplicated hypertensive vascular disease. Four patients received 10 mg. daily for 30 days; the fifth received 20 mg. daily for 50 days. Increase in weight and haemodilution were observed during the first 7 to 10 days. The blood pressure at rest increased slightly during the first week in all cases; in 3 it remained raised until the drug was discontinued; in the other 2, including the patient who received 20 mg. of the drug, blood pressure returned to the original figure after a transitory rise. Serum potassium and sodium decreased and serum carbon dioxide increased while the drug was being administered. It is concluded that the effect of DOCA is not due to a direct humoral mechanism. *A. Schott*

2145. **Blood Volume and Sympathectomy in Hypertension**
W. D. DAVIS and H. S. MAYERSON. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 117–120, May, 1948. 4 figs., 8 refs.

Blood volume changes were investigated in 20 patients with hypertension who had undergone sympathectomy; thoraco-lumbar sympathectomy was carried out in all the cases except 1, in which the transthoracic approach was used. There were 11 women and 9 men; their ages ranged from 22 to 50 years and the periods of follow up from 3 to 18 months. Plasma volume was measured photo-colorimetrically with the T 1824 dye; whole blood and red cell volumes were calculated from hematocrit readings (Wintrobe). No consistent post-operative changes in the blood volume were found, and no consistent deviation from "normal" values was observed pre-operatively. It was noted that in 5 patients in whom the red cell volume was low before operation the response to sympathectomy was poor, whereas in 5 patients in whom the red cell volume was normal, or above normal, the results were good. In patients with long-standing vascular disease there was a tendency to low blood volume. *A. Schott*

2146. **Osteoporosis Occurring During Potassium Thiocyanate Therapy for Hypertensive Disease**
J. J. HINCHEY, E. A. HINES, and R. K. GHORMLEY. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 548–554, May, 1948. 3 figs.

About 1 person in 50 taking potassium thiocyanate as a therapeutic measure in hypertension will develop osteoporosis. The authors suggest that anyone likely to benefit from potassium thiocyanate should also receive calcium in effective therapeutic doses at the same time.

[Why 1 in 50 should develop bone lesions is not at all clear and the present paper does not help. It is probable that potassium thiocyanate can be dangerous in any person suffering from a disorder of calcium metabolism. But this cannot be the whole story.] *G. F. Walker*

2147. **Pheochromocytomas Coexisting in Adrenal Gland and Retroperitoneal Space, with Sustained Hypertension. Report of a Case with Surgical Cure**
E. J. GANEM and G. F. CAHILL. *New England Journal of Medicine* [*New Engl. J. Med.*] **238**, 692–697, May 13, 1948. 2 figs., 27 refs.

A girl aged 12 had a 2-years' history of excessive perspiration and increased appetite, thirst, fatigue, palpitation, and occasional numbness and tingling in arms. Examination revealed an undernourished, emotionally unstable girl, with hypertension (180/120), tachycardia (120), and raised basal metabolic rate (B.M.R.) (51 to 67·6%), serum cholesterol 215 mg. per 100 ml., and, on *x*-ray investigation, a tiny area of calcification in the left suprarenal area. Nine months later the blood pressure had risen to 200/150 and there was well-marked hypertensive retinopathy. There had been no episodes suggestive of paroxysmal hypertension. Bilateral perirenal air insufflation showed a left suprarenal tumour, which was removed through an extraperitoneal lumbar approach. During operation manipulation of the tumour, which was intra-adrenal, caused the blood pressure to rise from 170/120 to 200/160 and the pulse from 130 to 170; after removal of the tumour the blood pressure fell to 60/30 and both adrenaline and adrenal cortical extract were administered. The tumour, which weighed 6 g., proved to be a benign phaeochromocytoma and contained adrenaline. After it was removed the blood pressure remained raised, averaging 160/144, although excessive sweating had ceased. Eight weeks after the first operation, at which a second mass had been suspected, a tumour was removed from the left retroperitoneal space through a left subcostal oblique transperitoneal incision. Histologically this tumour was the same as the intra-adrenal tumour removed at the first operation. A year and a half after the second operation the girl was in excellent health, blood pressure was 116/78, B.M.R. +5%, the retinopathy had disappeared, and the visual acuity had returned to normal.

Appended to this case report are critical observations on previously recorded cases, and an account of the depressor effect of 1164F—dimethyl piperidoaminomethyl benzodioxane—on this patient between her operations, which suggests that it might be of help in the diagnosis of hyperadrenalinaemia. *Henry Cohen*

2148. **Hormonal Hypertension and Nephrosclerosis as Influenced by the Diet**
P. DONTIGNY, E. C. HAY, J. L. PRADO, and H. SELYE. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 442–447, April, 1948. 17 refs.

Renal changes characterized by enlarged hyalinized glomeruli, formation of hyaline casts, dilated tubules, and thickening with necrosis of arteriolar walls, are produced in rats treated with lyophilized anterior pituitary extract (LAP) under certain conditions or with desoxycorticosterone acetate (DOCA), or by chronic non-specific stresses. The changes resemble those present in malignant hypertension and are referred to as nephrosclerosis: after DOCA overdosage or in chronic stress they are accompanied by hypertension. The present investigation concerns the relation of LAP nephrosclerosis to hypertension, and the aetiological role of a high-protein diet in hypertension; for LAP nephrosclerosis such a diet is known to be indispensable. LAP was given in doses of 20 mg. in 10% alcohol twice daily for 3 weeks to 4 series of rats all receiving diets almost optimal except for high sodium content; two series were controls, one received a 30% casein diet and one a 15% casein diet, and all had vitamin-B supplements. After 21 days the blood pressure was estimated and the animals killed. The extent and degree of the nephrosclerosis was determined and the kidneys and adrenals were weighed. It appeared that the production of nephrosclerosis by LAP overdosage was related to the 30% casein content of the diet and was associated with hypertension, nephrosclerosis and hypertension being very infrequent with the 15% casein diet and absent in animals not given LAP. In the control groups unilateral nephrectomy produced a

statistical difference between animals on the 15% and 30% casein diets, intact animals showing no difference. Hypertension was accompanied by statistically significant adrenal enlargement, which was not related to the casein content of the diet unless accompanied by administration of LAP. In a further series of experiments of the same type the amount of vitamin-B substances was increased generally and individually. Increase to 10 times the normal amount of vitamin mixture or choline chloride reduced the hypertension but not the nephrosclerosis. The theory that non-specific stress produces hypertension through the pituitary is restated. This process involves also the adrenals by a secondary effect which is markedly enhanced by a high-protein diet on which the adrenals enlarge or by which mineralocorticoid production is raised to the hypertension-producing threshold. Hypertension due to DOCA, in experiments now in progress, has not been affected by diet in the same manner as is LAP hypertension. It appears that in LAP hypertension the important role of the high-protein diet is to permit a pronounced enlargement of the adrenals. The results obtained with choline chloride are not thought to throw any light on the renal lesions produced by choline deficiency.

W. A. Bourne

BLOOD VESSELS

2149. **Two Cases of Periarteritis Nodosa. With Observations on Aetiology, Diagnosis, and Treatment**
J. M. SUTHERLAND. *British Medical Journal* [*Brit. med. J.*] **1**, 832–835, May 1, 1948. 20 refs.

A man aged 43 had widespread pains and pyrexia; there was tenderness and rigidity of the epigastrium, and both lumbar regions; the muscles of the legs were also tender. Painful subcutaneous nodules were present on the abdominal wall; one of these on section showed changes in the vessels characteristic of periarteritis nodosa. Further investigation revealed a leucocytosis, high erythrocyte sedimentation rate, and slurred QRS in the electrocardiogram. Later in the course of the illness albumin, erythrocytes, and granular casts appeared in the urine, blood was passed in the stools, and a retinal haemorrhage occurred. In treatment 2 antihistamine preparations were used, " benadryl " and " lertigon " (histamine azo-protein). Benadryl in doses of 50 mg. 4 times daily did not appear to have a beneficial effect, but after lertigon had been given in addition (1 ml. subcutaneously weekly) there were no exacerbations of the disease. Thirteen months after discharge from hospital the patient is at work, his weight is stationary, and the erythrocyte sedimentation rate is normal, but there is some evidence that hypertension is developing.

A woman of 52 had pain in the limbs and neck, weakness, and loss of weight. The temperature was raised for some months to a maximum of 101·5° F. (38·6° C.); it then returned to normal. The erythrocyte sedimentation rate was high; occult blood was present in the faeces. A radiograph of the chest showed no gross lesion. There was temporary improvement, but 10 months after the onset of the illness herpes zoster developed on the right chest wall; haemoptysis and vomiting then occurred. At this time there was emaciation and anaemia, with rales in the right lung and tachycardia. The blood pressure and temperature were normal. A radiograph showed opacities in the lungs suggesting active tuberculosis. The patient died suddenly and necropsy revealed lesions of periarteritis nodosa in the lungs and many of the abdominal viscera. There was patchy increase of density in the lungs, considered to be due to haemorrhage, the immediate cause of death being regarded as renal damage.

[The condition described in this paper is here referred to as periarteritis nodosa but this is inaccurate from the pathological point of view. All coats of the artery are involved, with periarteritis as a later change; hence the term polyarteritis nodosa is now more generally used.]

S. H. Cookson

2150. **Influence of Sodium Tetrathionate on Rate of Blood Flow to the Digits**
T. WINSOR. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 34–39, May, 1948. 5 figs., 7 refs.

Because of conflicting views about the value of sodium tetrathionate in the treatment of peripheral vascular disorders, as used by Theis and Freeland (*Surgery*, 1942, **11**, 101) the author investigated the effect of this preparation in 10 normal individuals and 10 patients with arteriosclerotic obliterative disease of the legs who had had a left lumbar sympathectomy. The rate of blood flow was determined by means of a digital plethysmograph (Burch, *Amer. Heart J.*, 1947, **33**, 48); skin temperatures were recorded by an automatic recorder from the left index finger and the left and right big toes, and pulse rates determined from the plethysmogram. The effect of sodium tetrathionate (0·6 g. intravenously) was compared with that of 5 ml. of distilled water and of placing the arm in water at 45° C. for 20 minutes. In the normal individuals sodium tetrathionate produced a slight but definite increase in the rate of flow, more pronounced in the finger than in the toes, but considerably less than that due to immersion of one arm in hot water. In the patients with vascular disease the flow rates in the lower limbs did not show any significant change, and those in the finger increased slightly but less than in the normal controls. Indirect heating increased the flow rates more than did the drug. The skin temperature increased in the controls by 1·1, 1·6, and 0·6° C. in the left index finger and left and right big toes respectively (maximum after 80 minutes) and by a further 1·7, 2·6, and 3·3° C. respectively as a result of indirect heating. In the patients with vascular disease no significant rise in skin temperature was produced by sodium tetrathionate in the non-sympathectomized lower limb, and a rise of less than 0·5° C. in the sympathectomized one. Indirect heating increased the temperatures by 4·1, 1·6, and 2·8° C. in the left index finger and left and right toes respectively. The drug produced a very slight decrease in the pulse rate. It is concluded that indirect heating is more efficacious than sodium tetrathionate in increasing the flow rate and skin temperature.

A. Schott

Disorders of the Blood

2151. **The Haematopoietic System in Mental Disorders.** (Le système hématopoiétique dans les affections mentales) J. ALEKSANDROWICZ and M. SPISS. *Sang* [*Sang*] **18**, 325–333, 1947. 21 refs.

After a review of the literature on blood changes associated with various psychoses and a discussion of the relation of the midbrain to erythropoiesis, the authors describe their observations on the marrow, obtained by sternal puncture. [There is no reference to the myelotropic hormone of Petrescu and Olaru (*Bull. Mém. Soc. Hôp. Bucarest*, 1945) which is alleged to be secreted by the anterior pituitary under the influence of the diencephalic nuclei.] It is alleged that the number of nucleated elements per c.mm. of marrow is, normally, between 40,000 and 150,000. [This great variation has caused many haematologists to ignore such counts.] In depressive states, the numbers are at, but not below, the lower limits of normal, while, in maniacal cyclothymic psychoses, they are greatly increased (between 277,000 and 500,000 in the authors' 13 cases). The hyperplasia of the marrow affects all types of cells, although, in some cases, there is a slight excess of reticuloendothelial elements, with a slight immaturity of the myelogram as a whole. The hyperplasia retrogresses when depression develops, but the authors are not convinced that the hyperplasia during the maniacal phases is necessarily the result of the leucocytosis that occurs in the peripheral blood in these cases, as in all conditions accompanied by violent and prolonged muscular work. Unfortunately, the marrow during, and after, hard muscular work has not been investigated in normal subjects. *A. Piney*

2152. ***In vitro* Study of Bone Marrow. III. Erythropoiesis *in vitro* of Sternal Marrow from Cases of Pernicious Anemia and Lymphatic Leukosis Under Therapy**
J. CLEMMESEN, T. ESPERSEN, and C. M. PLUM. *Blood* [*Blood*] **3**, 155–164, Feb., 1948. 2 figs., 5 refs.

Using a technique for keeping alive for several hours a suspension of marrow cells the authors have examined normal and certain types of abnormal erythropoiesis. The intermediate layers of cells from immediately centrifuged aspirated citrated sternal marrow were suspended in Locke's fluid with 1% of serum and incubated at 37° C. between concentric collodion membranes, through which nutrient Locke's fluid with 2% of serum was continuously circulated, and in a current of carbogen. Erythropoietic activity was expressed as the number of non-nucleated cells produced during 1 hour per nucleated red cell present before cultivation. In 31 normal persons specimens of marrow examined singly and nourished by the patient's own serum gave an average figure for erythropoietic activity of $5{\cdot}13 \pm 0{\cdot}26$. In cross-experiments, nourishment of the marrow by the serum of another person reduced activity to about 85% of that in the homologous system. In two cases of slight anaemia there was no pronounced deviation from normal of erythropoietic activity.

A case of moderately severe pernicious anaemia was studied before treatment and after the reticulocyte response to liver extract. Normal marrow and corresponding serum were used for the cross-experiments on each occasion. Before treatment, the pathological marrow showed 62% erythropoietic activity with its own serum, compared with normal marrow and serum. The percentage erythropoietic activity when the marrow was nourished by normal serum was increased to 152% of that with autologous serum, in contradistinction to the fall in activity of normal marrow nourished on alien serum. Further, normal marrow nourished on the pathological serum had only 67% of its usual activity. After treatment the activity of the patient's marrow with its own serum was 84% that of the normal marrow-serum system; the patient's marrow with normal serum had now 115% of the activity with its own serum, and normal marrow with patient's serum had 80% of the activity with its own serum. All values thus tend to become more normal.

The erythropoietic activity in two cases of lymphatic leucosis was studied before, during, and after urethane treatment supplemented by folic acid. The results indicate a deviation from normal similar to that found in pernicious anaemia, and become more normal after therapy. In the two cases, the erythropoietic activity of the marrow before treatment was 45 and 60% of the normal control systems, the samples of pathological marrow with normal serum showed 147 and 138% of their activities with their own sera, and the pathological sera reduced normal marrow activity to 64 and 67% respectively. During treatment these values became more normal, and after treatment were 94 and 80%, 102 and 120%, 90 and 85% respectively compared with the figures above.

As regards the significance of these figures, the authors consider that cells in fluid media can be counted with a considerable degree of accuracy, this being greater than is generally supposed. They also point to the influence of therapy on the results, which is unlikely to be accidental. *J. C. White*

2153. **Eosinopenia Caused by Adrenaline Infusion and by Insulin Hypoglycaemia**
Z. Z. GODLOWSKI. *British Medical Journal* [*Brit. med. J.*] **1**, 46–48, Jan. 10, 1948. 2 figs., 9 refs.

The author had found that insulin hypoglycaemia often improves allergic bronchial asthma. Eosinopenia, with a slow oscillating return of eosinophil counts to normal, was observed during successful treatment. Considerations suggesting that this phenomenon is due to

the outpouring of adrenaline are put forward in this paper, based on the study of 11 allergic and eosinophilic subjects (9 with bronchial asthma, 1 with urticaria, and 1 with dermatitis).

After determination of eosinophils in blood when the patient was not fasting, 8 to 10 mg. of adrenaline in 200 to 300 ml. of normal saline was given intravenously over 8 to 12 hours. Eosinophils were estimated half-hourly for 3 hours, then hourly until the patient fell asleep, then twice in 2 hours without waking the patient; 2 to 3 days later the insulin test was performed after a 12-hour fast with 100 units of soluble insulin, the same examinations being repeated. Sternal puncture before and during the eighth hour of the tests was performed on 7 cases. During adrenaline infusion, eosinopenia was marked after a few hours. After discontinuation of the infusion, the eosinopenia remained but decreased during the first hour of sleep, and normal values were attained 24 hours from the start. The eosinopenia was similar during insulin hypoglycaemia, but developed more gradually and did not persist for so long, the count rising rapidly during the first 2 hours of sleep. A common mechanism in these 2 conditions seems probable, and it is known that adrenaline is released in insulin hypoglycaemia.

The sternal marrow in the cases examined showed no change in eosinophil content when there was eosinopenia in the blood, appearing to be unaffected by adrenaline, and not to store the eosinophils withdrawn from the blood. Although the effect of injected adrenaline on the sympathetic system is quickly exhausted, eosinopenia may be a prolonged sympathetic effect. Eosinophilia is associated with vagal action. In sleep vagal preponderance neutralizes the eosinopenia due to transient sympathetic overactivity, but for return to the original condition of the blood sleep of more than 2 hours' duration is required. *J. C. White*

2154. **Clinical Tolerance to Nitrogen Mustards. (40 Observations.)** (Tolérance clinique des analogues de l'ypérite (moutardes à l'azote). (Etude basée sur 40 observations))
L. JUSTIN-BESANÇON, S. LAMOTTE-BARILLON, and C. POLONOVSKI. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **64**, 569–576, May, 1948.

Having treated 40 cases with nitrogen mustard, the authors discuss in some detail what they describe as the clinical tolerance for this group of drugs. They consider that their toxicity for the epithelium of the digestive tract, the gonads, and the bone marrow, and the small margin between the effective and the toxic dose, make it essential to treat only the right type of case and to proceed with the utmost caution. They do not consider it justifiable to give the nitrogen mustards in anything but malignant conditions, such as Hodgkin's disease. They describe in detail their own method of treatment, insisting that nitrogen mustard should not be given unless 2 months have elapsed since the last session of *x*-ray therapy and that the latter should not be instituted immediately after treatment with nitrogen mustard. The possible toxic effects observed by the authors are in general agreement with those noted by other workers. The immediate unpleasant generalized reaction after injection, they suggest, may be in part prevented by previous medication with opiates or barbiturates.

Janet Vaughan

2155. **Clinical Indications for Treatment with Nitrogen Mustards. (40 Observations.)** (Indications cliniques du traitement par les analogues de l'ypérite. Résultats qu'on peut en attendre. (Étude basée sur 40 observations))
L. JUSTIN-BESANÇON, S. LAMOTTE-BARILLON, and C. POLONOVSKI. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **64**, 576–582, May, 1948. 13 refs.

The authors describe the results of their treatment of 40 cases of different blood diseases with nitrogen mustard, using methyl-*bis*-(β-chloroethyl)-amine. They conclude that this drug can only be regarded as a palliative and never a cure, and that to obtain satisfactory results cases must be chosen carefully and observed closely both clinically and haematologically throughout the period of treatment. Like other workers with nitrogen mustard, they achieved the best results in certain cases of Hodgkin's disease. In their experience cases in "a satisfactory general condition" are most suitable for treatment. Severe anaemia, generalized bone pain, and the terminal stages are contraindications to the use of nitrogen mustard. They comment on the immediate improvement and sense of well-being that may follow the use of nitrogen mustards, so different from the malaise that may result immediately from *x*-ray therapy, and stress the value of these drugs in cases resistant to *x* rays.

Janet Vaughan

2156. **Adsorption of Bacterial Polysaccharides to Erythrocytes**
E. V. KEOGH, E. A. NORTH, and M. F. WARBURTON. *Nature* [*Nature, Lond.*] **161**, 687–688, May 1, 1948. 5 refs.

The authors have previously reported that saline extracts of smooth strains of *Haemophilus influenzae* contain a substance which is adsorbed to erythrocytes and makes these cells agglutinable by type-specific antisera. The sample of type-specific polysaccharide originally tested adsorbed from immune sera their power of agglutinating sensitized erythrocytes, but was unable itself to sensitize cells. It has now been shown that this result was due to the degradation of the polysaccharide used. By phenol extraction a water-soluble, phenol-insoluble fraction containing the type-specific polysaccharide was obtained, capable of being adsorbed to erythrocytes. This fraction could be degraded by treatment with dilute acid or alkali, losing successively its ability to be adsorbed, its property of precipitation with antibody, and, finally, its power of combination with antibody. Polysaccharides, adsorbable to erythrocytes, have been similarly prepared from a number of other bacteria. They form useful reagents for a number of immunological procedures, such as the titration of antibody in rabbit

antisera to be used for the treatment of influenzal meningitis. Human or fowl erythrocytes are sensitized by adding 1 volume of packed cells to 10 volumes of a 0·1% solution of polysaccharide. A 5% suspension in saline is used for the tests after washing the cells twice. One volume of cells and 10 volumes of graded dilutions of antiserum are mixed and the presence of haemagglutination is noted. *D. G. ff. Edward*

ANAEMIAS

2157. **Folic Acid**
J. F. WILKINSON. *British Medical Journal* [*Brit. med. J.*] **1**, 822–827, May 1, 1948. Bibliography.

The action of folic acid (pteroylglutamic acid) in conditions other than pernicious anaemia is discussed. In 3 patients with idiopathic steatorrhoea (non-tropical sprue) the response was good, but all relapsed later. One patient with coeliac disease did not respond at all. This confirms the reports of other workers that in non-tropical sprue treatment with folic acid is much less certain and effective than it is in the West Indian tropical sprue reported by Spies and others. The results in ulcerative colitis were poor, there being no improvement in the blood or intestinal functions. Negative results were also obtained in patients with aplastic anaemia, agranulocytosis, chronic neutropenia, and leuco-erythroblastic anaemia. In leukaemia, whether acute or chronic, folic acid does not influence the anaemia. In 2 patients who had had pernicious anaemia for many years and who developed chronic myeloid leukaemia there was, as might be expected, a temporary improvement on folic-acid treatment, but later these patients relapsed

The evidence that has accumulated makes it clear that, in general, only those anaemias in which there is megaloblastic marrow change respond to folic acid, while those in which the marrow is normoblastic or hypoplastic do not respond. The relative failure in non-tropical sprue suggests that in the cases described by the American workers there were gross nutritional deficiencies with superimposed gastro-intestinal disturbances, while those described by the British workers were primarily due to failure of absorption from the intestinal tract or failure to utilize nutritional factors, especially members of the vitamin B group.

The author considers that although the results with folic acid in pernicious anaemia appear good, they are not so satisfactory as those obtained with liver extracts or stomach preparations, quite apart from the danger of cord changes developing in patients given folic acid alone. There is a tendency to relapse, and for macrocytosis to remain. The very real risk of the development of cord changes means that folic acid alone is not safe treatment for pernicious anaemia. The use of " blunderbuss " mixtures of folic acid with liver, stomach, and iron, is especially deprecated, and the author points out that many of these proprietary mixtures do not contain the individual constituents in adequate doses. On the other hand, for the treatment of other macrocytic anaemias and achrestic anaemia, where there is no danger of cord changes, folic acid can be given with advantage, though it is still relatively expensive.

The efforts of Spies and others to find other substances analagous to folic acid are reviewed; so far only thymine (5-methyluracil) has been active. The author tried 5-methyl*iso*cytosine (amino-thymine) and found that this gave a partial response, but the dose was probably too small.

The author points out that pteroylglutamic acid is not Castle's extrinsic factor, because it can be given parenterally without previous digestion with gastric juice. It has different properties from the active stomach enzyme, haemopoietin, and it is not the anti-anaemic liver principle, since active liver extracts can be prepared almost free from folic acid; it also cannot be the factor that combats subacute combined degeneration of the spinal cord—if, in fact, this is a separate factor.

The results of treatment with folic acid conjugates are reviewed. The reports are so far contradictory, possibly because the doses employed by some workers were too small.

[This is the second part of an article; the first part appeared in the *British Medical Journal* of April 24, 1948, and an abstract was published in *Abstracts of World Medicine*, 1948, **4**, 399.] *M.C. G. Israëls*

2158. **Anaemia Associated with Trauma and Sepsis**
J. VAUGHAN. *British Medical Journal* [*Brit. med. J.*] **1**, 35–39, Jan. 10, 1948. 66 refs.

The morphology of the anaemias and the metabolic disturbances are similar in states of sepsis and in trauma. Interference with haemoglobin synthesis appears to be a common factor.

The anaemias accompanying acute and chronic infections are better distinguished by the kind of infection than by its duration. Fulminating *Clostridium welchii* infections may produce haemolytic megalocytic anaemias. In most chronic, and the non-fulminating, infections the anaemia is normocytic and normochromic, but may be microcytic and hypochromic if of long standing. The bone marrow is active. The metabolic disturbances are reflected in the low plasma iron level, high serum copper level, high erythrocyte protoporphyrin III, and increased excretion of coproporphyrins I and III. Serum bilirubin and the urobilinogen output are usually normal, but there is a negative nitrogen balance with high urinary output of ammonia and urea. Similar metabolic changes accompany experimentally produced sterile abscesses. Anaemia may occur not only in severe casualties but also after slight injuries with trivial blood loss and after operations not preceded by trauma. Little is known of the accompanying metabolic disturbances except that the plasma proteins often fall and that there is a high urinary nitrogen output, partly diminished by giving a high-protein diet.

In considering the aetiology of these anaemias it is apparent that breakdown of tissues is a factor common to states of sepsis, trauma, and experimental sterile abscesses. The marrow is not aplastic, and haemolysis is not usually a feature. Lack of haematopoietic factors is a common cause of dyserythropoiesis, but the well-recognized factors are not effective in treatment in these cases. Cobalt possibly plays a part in the synthesis of

haematin or in the union of haematin and globin. In these anaemic states, there is failure to utilize iron but no lack of iron, and formation of porphyrins from pyrrole precursors also does not appear to be disturbed. There is a disturbance of protein metabolism, and a conditioned deficiency of certain amino-acids necessary for globin formation may be brought about, possibly through liver damage or by depletion of the body reserves of amino-acids by the demands of damaged tissues.

In treatment, iron and liver are ineffective in general, and the position of cobalt is uncertain. A high-calorie high-protein diet should be given, with attention to the patient's capacity for assimilation. Blood transfusion remains the only effective means of restoring the erythrocytes. *J. C. White*

2159. **Megaloblastic Anaemia of Pregnancy. Report of an Unusual Case**
M. GILLESPIE and A. M. RAMSAY. *British Medical Journal* [*Brit. med. J.*] **1**, 828–830, May 1, 1948. 1 fig., 8 refs.

The authors describe an unusual case which they consider is an example of megaloblastic anaemia of pregnancy. When the patient was first seen a few days after delivery the profound anaemia was associated with a leucopenia and a high proportion of immature granulocytes, which suggested the diagnosis of acute leukaemia. Sternal marrow puncture, however, revealed a myeloid: erythroblast ratio of 1·5 : 1 and the presence of megaloblasts. Intensive treatment with liver extract and proteolysed liver was without effect and the patient died. At necropsy there was intensive hyperplasia of the marrow, the predominant cell being of " the primitive haemocytoblast variety " with many megaloblasts. In an addendum the authors refer briefly to a somewhat similar case unassociated with pregnancy in which they believe that the precipitating factor was excessive dosage of a sulphonamide, 70 g. of which were given over a period of 5 weeks for acute tonsillitis. In neither case was folic acid administered. *Janet Vaughan*

2160. **Folic Acid and the Cholinesterases**
R. D. HAWKINS. *Archives of Biochemistry* [*Arch. Biochem.*] **17**, 97–104, April, 1948. 9 refs.

The possible effect of folic acid on cholinesterase or pseudo-cholinesterase activity *in vitro* and *in vivo* was investigated because of the demonstration (Davis, *Science*, 1946, **104**, 37; *Amer. J. Physiol.*, 1946, **147**, 404; *Proc. Soc. exp. Biol., N.Y.*, 1946, **63**, 287) of production in dogs by oral choline or acetylcholine of hyperchromic anaemia curable by liver extract or pteroylglutamic acid, of the increased " acetylcholine-like activity" of the anaemic serum and its diminution by treatment and anti-anaemic substances, and of the increase in plasma cholinesterase activity of dog and human serum by liver and pteroylglutamic acid.

Male rats of the Wistar strain were used to investigate the effect of dietary intake of folic acid on the activity of true cholinesterase and pseudo-cholinesterase. After a 10-week experimental period, no significant difference between the activities of either of these enzymes was found in rats fed on a diet deficient in folic acid and on a diet with a daily supplement of 25 μg. of folic acid. Further, samples of plasma from the two groups were divided and incubated for 2½ hours at 37° C., one portion with 0·15 mg. of folic acid per ml. and the other with water. No increase in activity of the two enzymes was found in the plasma of either group incubated with folic acid. Enzymatic activities were measured by the Warburg manometer at 37° C., 0·03 molar acetyl-β-methylcholine and 0·006 molar benzoylcholine being used respectively as substrates for cholinesterase and pseudo-cholinesterase.

To determine whether factors other than folic acid might be responsible for increased ability of anaemic dog plasma to hydrolyse acetylcholine after incubation with folic acid, samples of plasma from two groups of dogs maintained on different diets for 3 months were examined for cholinesterase activity before and after incubation with folic acid. In one group the diet was that used by Davis, in the other group a diet including dried yeast was used. No difference in activity was found in the two groups before and after incubation with 0·15 mg. of folic acid per ml. for 2½ hours at 37° C. Two dogs in the first group were also given 15 mg. of folic acid orally; there was no change in activity of the two enzymes after 5 hours.

Oral administration of 15 mg. of synthetic folic acid to 5 normal human males failed to alter significantly the cholinesterase or pseudo-cholinesterase activity after 5 hours. The experiments provide no evidence that folic acid increases the cholinesterase activity of the body. *J. C. White*

2161. **Infantile Form of Pernicious (Addisonian) Anemia. Report of a Long Term Study of a Case**
B. BENJAMIN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **75**, 143–189, Feb., 1948. 19 figs., 19 refs.

The author reports prolonged, detailed, and extensive investigations of a child who developed an Addisonian type of anaemia in the second year of life. The condition responded well to liver therapy, but has required continuous treatment ever since to avoid relapses. It is thus a different disease from the rather commoner macrocytic anaemia of infancy which after treatment with liver or folic acid does not require continuous therapy. The author concludes that his case is one of pernicious anaemia due to congenital absence of the intrinsic factor in the gastric secretions. *N. M. Jacoby*

LEUKAEMIAS

2162. **Pulmonary Edema in Leucemic Mice Following Treatment with Urethane**
W. W. WINCHESTER and G. M. HIGGINS. *Science* [*Science*] **107**, 568–569, May 28, 1948. 7 refs.

Experiments were conducted with a transmissible strain of myelogenous leukaemia in mice. As a control, similar doses of urethane were given to normal mice of

the same strain as the leukaemic mice. An important criterion for judging the effectiveness of the urethane treatment of the leukaemia was the life-span of the animals. In the first series of animals treated three-quarters died of pneumonia, and when sections were studied it was found that this pneumonia was secondary to a mild pulmonary oedema in all the animals. A second series of mice given larger doses of urethane developed a more severe and more rapidly fatal type of pulmonary oedema. Similar oedema occurred in the normal mice given large doses of urethane. In a third series of leukaemic mice, an unsuccessful attempt was made to adjust the dose of urethane so that the leukaemia could be controlled without production of pulmonary oedema. At necropsy the thorax contained fluid, the alveoli and bronchi were distended with homogeneous material, and there was capillary engorgement with rupture. Localized oedema was also noted in other regions.

In the literature there are reports that urethane increases capillary permeability; this has been attributed to capillary dilatation as well as to a direct toxic effect. The present authors are aware that these results may not be applicable to man, but they think that such phenomena should be looked for. [No such effects have been reported so far in human beings receiving urethane in therapeutic doses.] *M. C. G. Israëls*

2163. **Use of Folic Acid Derivatives in the Treatment of Human Leukemia**

L. M. MEYER. *Transactions of the New York Academy of Sciences* [*Trans. N.Y. Acad. Sci.*] **10**, 99–103, Jan., 1948.

" Teropterin " (pteroyltriglutamic acid), in doses of up to 200 mg. per day, was used for the treatment of human leukaemia. Most patients with chronic lymphocytic leukaemia (7 cases) experienced an increased sense of well-being and felt stronger but no significant changes in blood or bone marrow and no regressions in lymph nodes, liver, or spleen were observed. The most dramatic results were obtained in two cases of multiple myeloma; the patients were relieved of pain and able to get out of bed in 2 to 3 weeks. The improvement, however, was entirely subjective and the physical signs were unchanged. In one case of acute lymphoblastic leukaemia, the number of circulating lymphoblasts decreased and that of lymphocytes increased, and the clinical picture suggested a chronic lymphocytic leukaemia but the patient soon died.

Eight other patients were treated with anti-folic acid compounds. Three patients with chronic lymphocytic leukaemia felt better but there was no improvement in the blood counts. In 3 of 5 cases of acute leukaemia, there was a reduction in the total white cell count and a temporary shift to the right. The remission though short-lived suggested an alteration in, or interference with, the metabolism or chemical reaction in the malignant cells.

[In a discussion of this and accompanying papers Gellhorn expressed the opinion that there was no evidence that the course of the disease had been in any way altered by teropterin with the doubtful exception of one case of carcinoma of the prostate. He recognized, however, the apparent analgesic effect and that a sense of well-being was produced, and suggested that the subjective improvement might be due to an effect of the drug on the central nervous system related to the pharmacological action of glutamic acid.] *L. Foulds*

2164. **Aleukemic Myelosis: Chronic Nonleukemic Myelosis, Agnogenic Myeloid Metaplasia, Osteosclerosis, Leukoerythroblastic Anemia, and Synonymous Designations**

E. L. HELLER, M. G. LEWISOHN, and W. E. PALIN. *American Journal of Pathology* [*Amer. J. Path.*] **23**, 327–366, May, 1947. 13 figs., 76 refs.

Three cases of aleukaemic myelosis are reported. The study of these cases, together with a review of the literature, led the authors to the conclusion that this disease is really a form of myelogenous leukaemia, although many cases of this type are genuinely aleukaemic. The leukaemic nature of this disorder has not been generally recognized because of atypical clinical, haematological, and pathological features; moreover, its identity has been obscured by the diverse terminology used by the various investigators. Aleukaemic myelosis appears to be an appropriate designation for this disease, characterized by splenomegaly and non-specific alterations in the blood. In the opinion of the authors the criteria alleged to differentiate aleukaemic myelosis from leukaemia do not withstand critical analysis. Osteosclerosis may occur in myelogenous leukaemia, but its occurrence favours the development of an aleukaemic state of the blood. The Malpighian corpuscles in the spleen may be intact or partially or completely destroyed in both aleukaemic myelosis and myelogenous leukaemia. Cases of the type reported present strong evidence for the view that much of the myeloid reaction in the spleen, liver, and lymph nodes in myelogenous leukaemia is not the result of metastasis but of myeloid transmutation of the local reticulo-endothelial system in these organs.

G. Popják

2165. **Similarity to Heparin of the Clotting Inhibitor in Acute Leucemia and the Significance of Hyperheparinemia in Estrapenic Cholinergic States**

R. D. BARNARD. *Science* [*Science*] **107**, 571–572, May 28, 1948. 1 fig., 8 refs.

It has been reported that heparin is increased in the blood in patients with pernicious anaemia and leukaemias, in anaphylactic and peptone shock, and in radiation sickness in dogs. The usual methods for its identification are neutralization by thrombin or globin, and the reaction with toluidine blue. In this paper evidence is given that heparin was increased in the blood in 5 cases of human leukaemia and two of " thrombotic cardiogenic shock ", by showing that plasma from these patients added to normal citrated human plasma caused a dissociation in the precipitation rates of filiar and gelatinous plasma when the plasma was clotted by calcium chloride and viper venom. Such dissociation usually means that heparin is present in a concentration of about 2 mg. per 100 ml. Thrombin titrations gave similar results.

Hyperheparinaemia explains the incoagulability of the blood but does not explain the haemorrhagic diathesis present in these diseases. The author draws attention to the apparent limitation of hyperheparinaemic extravasation to conditions in which the cholinesterase concentration in blood is lower than normal. In these states there is usually a thromboplastin deficiency as well, and the author therefore suggests, although he brings no evidence in support, that the blood heparin only rises when there is inadequate thromboplastin to neutralize it and that extravasations are not in themselves due to the hyperheparinaemia. *M. C. G. Israëls*

2166. **Effects of Radioactive Sodium on Leukemia and Allied Diseases. Preliminary Report**
T. C. EVANS, M. LENZ, C. P. DONLAN, and M. J. LEMAY. *American Journal of Roentgenology and Radium Therapy* [*Amer. J. Roentgenol.*] **59**, 469–481, April, 1948. 9 figs., 18 refs.

Radioactive sodium was tested in 24 cases of chronic myelogenous leukaemia, acute and chronic lymphatic leukaemia, in polycythaemia vera, and in single cases of various generalized malignant conditions. The results justify the conclusion that the administration of radioactive sodium is an effective means of giving protracted whole-body irradiation. In a few individuals the radiation produced good results, but the response to radioactive sodium was poor in acute leukaemia, or when the radio-resistance of the pathological cells was high or when the haematopoietic system was already damaged. The rapidity and the degree of the response, as well as the duration of the recession of the symptoms, could usually be regulated by the amount of each dose of radioactive sodium and the frequency of the treatments. Very slight radiation sickness followed in only 2 cases. Radioactive sodium is effective when given by mouth. This avoids some of the complications observed with intravenous applications. In view of its short half-life (only 15 hours) the use of radioactive sodium must necessarily be limited to institutions situated near the source of supply. *A. Orley*

2167. **The Nature of Anaemia in Leukaemia**
D. H. COLLINS and W. MCI. ROSE. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **60**, 63–74, Jan., 1948. 8 figs., 28 refs.

Fifty cases of leukaemia (14 acute, 16 chronic lymphatic, and 20 chronic myelogenous) were examined haematologically in the Pathological Department, Leeds General Infirmary. The authors studied the coincident occurrence of anaemia, which was most severe in the acute forms of leukaemia and least severe in the chronic myelogenous types. Five cases are discussed in detail.

Nucleated red cells were observed less often in the peripheral blood in chronic lymphatic leukaemia, the severe anaemia being secondary to the lymphocyte infiltration of the bone marrow leading to hypoplasia. In all types of leukaemia there was some evidence in the early stages of abnormal activity of the red-cell-forming tissues, often antedating the leukaemic manifestations. The authors state that blood loss and extensive red cell destruction may aggravate the anaemia, but essentially there is hypoplasia in lymphatic leukaemia, and defective cell production from a hyperplastic marrow in myeloid leukaemia. The incidence and severity of the anaemia in these 50 patients are analysed. *John F. Wilkinson*

2168. **The Newer Nitrogen Mustards in the Treatment of Leukemia**
J. H. BURCHENAL. *Radiology* [*Radiology*] **50**, 494–499, April, 1948. 5 figs., 9 refs.

The nitrogen mustards in use have definite disadvantages: they are liable to cause troublesome nausea and vomiting and the remissions produced even in diseases such as chronic myeloid leukaemia which respond favourably rarely exceed 6 months. Related compounds are therefore being tested in order to discover those which are without unpleasant side-effects and which will give longer remissions. In this paper results are recorded with two related compounds: (*a*) 1,3-propanediamine-N,N,N′,N′,-tetrakis (2-chloroethyl) dihydrochloride, known as SK 136, and (*b*) SK 137, the similar diamine-2-chloro compound. SK 137 caused occasional transient psychoses lasting for 12 to 72 hours and was but little used. SK 136 in a dose of 0·1 mg. per kilo body weight for 4 to 8 doses caused little nausea and vomiting, especially in patients with chronic myeloid leukaemia, but there was slight transient dizziness. A dose larger than this did cause nausea, vomiting, and severe dizziness. SK 136 produced haematological and clinical responses similar to but no better than those with the usual nitrogen mustards. Patients with chronic myeloid leukaemia responded best; in 11 patients the white cell count decreased and in 10 there was subjective improvement; the haemoglobin level rose in 9, the spleen became smaller in 9, the leucocyte picture became more normal in 7, and remissions lasted from 1½ to 5 months. The results in 2 subacute and 19 cases of acute leukaemias were all much less favourable. [No results with Hodgkin's disease are recorded. The conclusion of the author that SK 136 has little advantage over the more usual compounds is fully justified, if disappointing.]
M. C. G. Israëls

2169. **Are the Basophilic Leucocytes " Heparinocytes "? Part I.** [In English]
G. TÖTTERMAN. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 176–182, 1948. 4 refs.

The metachromatic staining of basophil leucocytes suggests that the cell granules may be identical with heparin. A series of 88 cases of myeloid leukaemia were examined to test the hypothesis that basophilia may be associated with the haemorrhagic diathesis observed in some instances. In cases of acute myeloid leukaemia characterized by strong haemorrhagic diathesis the basophil count was very low. There was no difference in the incidence of bleeding tendencies in cases of chronic myeloid leukaemia, whether there was basophilia or not.
E. F. McCarthy

Respiratory Disorders

2170. **Idiopathic Pulmonary Haemosiderosis (Essential Brown Induration of the Lungs)**
W. G. WYLLIE, W. SHELDON, M. BODIAN, and A. BARLOW. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **27**, 25–48, Jan., 1948. 14 figs., 16 refs.

The authors present a series of 24 cases—17 from the literature and a further 7 seen between 1939 and 1947 at the Hospital for Sick Children, Great Ormond Street, London—and describe the symptoms, clinical and radiological findings, and treatment. The condition is fairly typical, and all the patients except one were under 16 years. Of the total of 24 cases, 18 had proved fatal up to the time of publication; 5 of the patients from Great Ormond Street were still living, but their condition was not considered satisfactory, and the radiological appearances were still abnormal.

From a study of this series it is concluded that the disease affects mainly the lesser circulation, it is not of a hereditary or familial nature, and the prognosis is poor. [The name of the condition is a little misleading, because although it calls attention to the symptoms, which are largely related to the lungs, it completely obscures the underlying pathology, which is presumably that of a haemolytic anaemia.] *F. P. Lee Lander*

2171. **Importance of Pressure Factors in the Genesis of Pulmonary Edema Following Vagotomy**
A. H. SUSSMAN, A. HEMINGWAY, and M. B. VISSCHER. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 585–588, March, 1948. 6 refs.

The question of vasomotor control through the vagi in relation to pulmonary oedema is still unsettled. Bilateral cervical vagotomy results, in several species of animals, in pulmonary oedema, but, according to Lorber (*J. exp. Med.*, 1939, **70**, 117) among others, obstruction to the airway by laryngeal paralysis and accumulation of tracheal secretions play a large part. Also, from the observations of Daly *et al.* (*Quart. J. exp. Phys.*, 1942, **31**, 211) the vasomotor influence of vagal fibres appears small. On the other hand, in Farber's (*Arch. Path.*, 1940, **30**, 180) experiments on guinea-pigs, maintained on positive pressure respiration (pressure conditions not recorded) fatal lung oedema occurred earlier in vagotomized animals than in those with intact vagi, and the conclusion was that "disturbances to the vasomotor control of the pulmonary vessels . . . lead to the production of severe pulmonary oedema and haemorrhage".

When the latter experiments were repeated during artificial respiration by positive-pressure tracheal cannula insufflation at two pressure levels, pulmonary oedema did not occur at a pressure of 6 mm. Hg within periods of from 5 to 25 hours but it did occur within 5 hours in both intact and vagotomized animals at 20 mm. Hg. Thus differences in pressure appeared to be the critical factors and vagotomy did augment pulmonary oedema at the high-pressure level, although it is admitted that an inhibiting influence of the vagi might occur at pressure levels intermediate between the two employed in the present study. *H. Pollak*

2172. **An Attempt to Produce Pulmonary Edema by Increased Intracranial Pressure**
A. SURTSHIN, L. N. KATZ, and S. RODBARD. *American Journal of Physiology* [*Amer. J. Physiol.*] **152**, 589–590, March, 1948. 8 refs.

Intracranial pressure in dogs was raised by intracranial injection of saline, which causes a rise in systemic blood pressure. In such conditions pulmonary oedema has been observed. The authors, however, suspected that the pulmonary oedema might be due to aspiration of saliva which was produced in considerable amounts by many of the animals. This view was supported by experiments on dogs with tracheal cannulae in which increased intracranial pressure failed to cause pulmonary oedema. A picture grossly resembling pulmonary oedema was seen in the dogs without tracheal cannulae. *H. Pollak*

2173. **A New Approach to the Understanding of Pulmonary Emphysema. A Method of Determining Emphysema of the Lungs**
G. G. ORNSTEIN. *Quarterly Bulletin of Sea View Hospital* [*Quart. Bull. Sea View Hosp.*] **9**, 89–136, April, 1947. 20 figs., 14 refs.

The author points out the difficulties in diagnosis and loose application of the term "emphysema", the chief symptoms of which are dyspnoea and fatigue on exertion, symptoms also present in other pulmonary and cardiac diseases. The latter conditions and hypertrophy, such as may occur in the healthy areas of lungs in association with massive fibrosis or atelectasis, or after lobectomy or pneumonectomy, may be differentiated from true emphysema by the fact that a diminished capacity for diffusion of oxygen and carbon dioxide is found in the emphysematous lung.

In the author's diffusion test, after a standard exercise (stepping up and down an 8-in. (20 cm.) step 30 times in 1 minute) the subject was connected for 20 seconds to a rebreathing bag containing 1 litre of air. Normal subjects used a fairly constant amount of oxygen and increased the volume of carbon dioxide in the rebreathing bag. The percentage volume of oxygen, initially 20·93, was reduced to a mean of $7{\cdot}95 \pm 0{\cdot}851$. Carbon dioxide increased from 0·03 volumes per cent. to $8{\cdot}09 \pm 0{\cdot}436$. In females the oxygen value was $8{\cdot}30 \pm 0{\cdot}714\%$ and the carbon dioxide value $7{\cdot}70 \pm 0{\cdot}497$. The finding of an oxygen value up to 9·5% was considered good, any figure lower very good. Figures above 10% indicated impaired permeability and diffusion.

The author also found that the most effective ventilatory test was to measure the resting minute ventilation of the subject under basal conditions and then the maximum breathing capacity for 1 minute; this was done by using either a spirometer, a Douglas bag, or a gasometer (resembling the one used in measuring illuminating gas). Before measurements are made the subject is asked to breathe normally into the apparatus for a short while and then to breathe as deeply and rapidly as possible for 30 seconds, and the maximum breathing capacity is recorded. The gasometer can also be used in recording the resting minute ventilation. Before recording this the subject should rest in a chair for 30 minutes. The volume of air used during the maximum breathing capacity test divided by the volume breathed during the test of resting minute ventilation, gives a measure of the ventilatory reserve. This was found to be about 20 for males and 13 for females.

Case histories and results of tests in 19 cases are given, together with the results of the function tests in 81 cases. It is concluded that ventilation plays no part in the ability of the alveolar spaces to carry on the interchange of carbon dioxide and oxygen. A lung may be enlarged and overdistended for many years without developing emphysema. The large bullous blebs sometimes seen at the base of the lungs on radiographs may lead to poor ventilation, having the same effects on the underlying diaphragm as an atelectasis of the lower lobe might have. They change volume slightly during inspiration and expiration and thus affect the diaphragm by reducing its mobility. Sub-pleural blebs may be present without any emphysema, are not due to this disease but to a rupture of the sub-pleural elastic fibres, and are outside the lung. The bullae are due to a rupture of the overdistended alveolar walls, and surgical procedures which remove either the bullae or the segments of the lungs to which the bullae are attached may improve the pulmonary ventilation. *E. H. Hudson*

2174. **Penicillin and Streptomycin Aerosol in the Treatment of Pulmonary Disease**
E. W. HAGENS, M. KARP, and C. J. FARMER. *Archives of Otolaryngology* [*Arch. Otolaryng., Chicago*] **47**, 138–148, Feb., 1948. 7 refs.

The effect of the inhalation of penicillin and streptomycin in pulmonary disease is reported. The equipment used consisted of an oro-nasal mask without valve, a nebulizer, and an oxygen tank. The solutions used were: (1) sodium penicillin 200,000 units per day, and (2) a mixed aerosol containing 200,000 units sodium penicillin and 500,000 units streptomycin in 25 ml. isotonic saline or distilled water. Sodium penicillin and streptomycin were mixed in one container. When calcium penicillin was used the solutions of penicillin and streptomycin had to be given in separate containers because calcium penicillin caused precipitation in the solution of streptomycin. There were 46 inhalation periods of about 5 minutes each in the 24 hours, 1·5 ml. aerosol being inhaled on each occasion. The rate of oxygen flow was about 7 litres per minute.

Ten patients were treated—4 with bronchiectasis, 2 with chronic bronchitis, and 4 with bronchial asthma. In all cases penicillin alone was inhaled for several days, and the mixed aerosol of penicillin and streptomycin was then given for 3 to 9 days. In 8 patients Gram-positive organisms disappeared from the sputum after several days of penicillin treatment. When streptomycin was added Gram-negative bacteria disappeared in 5 patients who were inhaling 500,000 units per day but persisted in 5 patients who were inhaling only 200,000 units per day. Clinically 9 of the patients were improved. This was most obvious in those with bronchiectasis in whom the sputum was reduced in quantity by a third or more and was less foul. Bronchoscopic examination in 3 patients before and after treatment revealed no significant change in the state of the bronchial mucosa. The results in 111 patients referred from other departments of the hospital for penicillin inhalations are mentioned. Many kinds of pulmonary disease were represented. The results were similar, patients with bronchiectasis showing most improvement. However the records were inadequate for detailed analysis. Reactions to penicillin occurred in 6 patients: 2 developed dermatitis and 1 complained of dizziness and 3 of dyspnoea after the inhalations.

Experiments on a volunteer showed that significant levels of penicillin developed in the blood only when solutions containing 50,000 units per ml. or more were inhaled and these irritated the throat. No streptomycin was detected in the blood even in a patient who was inhaling as much as 750,000 units per day. Analysis of the washings from the mask and rebreathing bag showed that about one-fifth of the penicillin remains in the apparatus after use. As some is also lost through the exhaling valve and some remains in the upper air passages, an amount considerably smaller than that nebulized actually reaches the lungs. *Arthur Willcox*

2175. **A Bronchoscopic and Auscultatory Study of Adventitious Sounds after Total Pneumonectomy.** (Contribution à l'étude des râles bronchiques: Constatations stéthacoustiques et bronchoscopiques après pneumonectomie totale chez l'homme)
M. FOURESTIER. *Presse Médicale* [*Pr. méd.*] **56**, 318–319, May 1, 1948.

The author describes a single case in which, immediately after a pneumonectomy had been performed, auscultation revealed the presence of many coarse rales and rhonchi equal in intensity over the whole of both hemithoraces. While the patient was still under the anaesthetic, bronchoscopy disclosed the presence of thick, stringy mucous in the region of the hypopharynx, the glottis, and vocal cords. The trachea and main bronchi were clear. Immediately the mucus was removed the adventitious sounds ceased, and there was the expected silence on the operated side. The sounds were heard again when mucus had once more collected and were audible over the whole of both sides. The author concludes from this that bronchial rales and rhonchi are transmitted by way of the chest wall, and that in consequence the topographical location of these sounds bears no relation to the location of the causative lesion.

[The fallacy in the conclusion would appear to be that the sounds heard were not bronchial in origin, but were, instead, similar sounds produced by mucus in the hypopharynx and glottis. That these sounds were transmitted by way of the chest wall would certainly appear to have been demonstrated, but this conclusion cannot necessarily be applied to sounds which actually originate in the bronchi themselves.]

Richard D. Tonkin

2176. **Primary Atypical Pneumonia. A Clinical Study**
J. W. STEPHENS. *Lancet* [*Lancet*] **1**, 703–707, May 8, 1948. 1 fig., 22 refs.

The author describes an outbreak of a febrile disease with pulmonary involvement in troops in the Naples area in March, 1946, 58 cases being observed, 44 of them in men from the same unit. Epidemiologically there was no relation to infective hepatitis. The hygienic arrangements were adequate; there was no evidence of bed-to-bed or room-to-room spread of the disease. The dates of onset were between March 4 and March 25, with a special preponderance between March 7 and March 11. Two cases in which the date of probable exposure to infection was known suggest an incubation period between 10 and 12 days.

Clinically, the onset was abrupt with severe headache, sweating, shivering, anorexia, and fever. In spite of the high temperature the general condition remained good. There was usually dry cough from the onset, though the patient made no special complaint about this. Most commonly on the second or third day, but sometimes earlier and sometimes later, abnormal physical signs appeared in the chest, consisting of localized areas of rhonchi or crepitations or signs of a mild generalized bronchitis. The crepitations might be very localized and require careful examination for their detection. The spleen was enlarged in 18 cases; it was firm and slightly tender. More rarely the liver might be enlarged. The cough was usually dry, and sputum, when present, was scanty; there was no frank haemoptysis but the sputum was blood-stained in 5 cases. The fever lasted between 4 and 11 days and usually settled by lysis. There was a relative bradycardia. Anorexia was noted in 37 cases, and vomiting, at the onset only, in 10. There was pain in the chest in 19 cases. Radiographically the right lung was involved more often than the left; in half the cases the lesions spread out fanwise from the hilum. The most common type of shadow was an homogeneous opacity with indefinite margins. Bilateral shadowings were seen in only 4 cases. The lesions usually resolved in 4 to 5 weeks.

The author stresses that the radiographic appearances should be regarded as confirmatory and that the diagnosis should be made on clinical grounds in most cases. The leucocyte count was generally within normal limits. No complications occurred except delirium tremens in one man who was a heavy drinker and thrombosis of the superficial veins of the calf in another. There was no mortality. In discussion the author mentions the demonstration by other workers that many of the outbreaks previously described as of "primary atypical pneumonia" in the Mediterranean area were due to Mediterranean Q fever, and it seems likely that his cases were of the same sort.

J. G. Scadding

2177. **Penicillin Aerosol in the Treatment of Experimental Pneumococcus Pneumonia**
F. P. HADLEY, A. P. MCILROY, and A. M. LAURENT. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 204–209, May, 1948. 18 refs.

Rats were used in this investigation and pneumonia was provoked by the intrabronchial inoculation of a virulent strain of pneumococcus. Typical lobar pneumonia resulted within 18 hours, accompanied by septicaemia and consolidation of the inoculated lobe; the average survival time was 42 hours. Both prophylactic and therapeutic experiments were carried out with penicillin aerosols. From 4 to 10 exposures were given, each of 15 minutes' duration, and the total amount of penicillin inhaled by each rat was estimated by multiplying the tidal air for rats in ml. per minute by the estimated amount of penicillin in each ml. of air delivered from the atomizer.

When the infection in rats was produced by pneumococci suspended in mucin, penicillin had no prophylactic effect whatsoever either by inhalation or parenterally, but inhalation of penicillin was very effective against infections produced by pneumococci suspended in broth (no adequate explanation is given). Four penicillin inhalations given at intervals of 2 hours (a total of 5,000 to 16,750 units) saved 73% of rats infected intrabronchially with 100 MLD of mucin-suspended pneumococci, compared with a survival rate of 9% for controls. Penicillin aerosols were as effective even when treatment was delayed for 18 hours so that lung consolidation and septicaemia were established.

R. Wien

2178. **Myocardial Metastasis by Bronchial Carcinoma and Other Neoplasms**
J. E. G. PEARSON. *British Journal of Tuberculosis* [*Brit. J. Tuberc.*] **42**, 31–38, April, 1948. 7 refs.

Invasion of the myocardium was found at necropsy or thoracotomy in 17 of 148 cases of bronchial carcinoma. In 11 of these an arrhythmia had been present (paroxysmal auricular fibrillation in 5, established auricular fibrillation in 2, auricular flutter in 2, paroxysmal auricular fibrillation and flutter in 1, and paroxysms of premature systoles in 1). Malignant deposits were found in the left auricle in 14, in the right auricle in 7, and in the left ventricle in 2, but never in the right ventricle. The auricular involvement was due to direct extension of the growth. In 3 cases the appearance of an arrhythmia led to a clinical diagnosis of myocardial metastasis. During the same 5-year period necropsy was performed on 358 patients who died from other forms of malignant disease. Myocardial involvement was found only in 19 cases, in half of which the ventricles alone were affected. An arrhythmia was recorded in only 1 of these cases.

Arthur Willcox

Digestive Disorders

2179. **The Diagnosis and Treatment of Gastric and Duodenal Ulcers of Syphilitic Origin.** (A lueses eredetű gyomor- és nyombélfekélyek diagnosztikája és therápiája)
L. KÜRTHI. *Orvosok Lapja* [*Orv. Lapja*] **4**, 586–589, May 2, 1948. 4 figs., 15 refs.

Of 3,066 cases of peptic ulcer observed in 16 years 52 (1·7%) were of syphilitic origin. The incidence was much higher among cases of gastric ulcer—41 out of 826 (4·9%)—than among cases of duodenal ulcer—11 out of 2,240 (0·5%). All 52 patients admitted syphilitic infection, but only 23 had received regular treatment. The serum reactions were positive in all cases, and, in a few, positive specific reactions were given by the gastric juice and cerebrospinal fluid. The symptoms were not different from those usual in ulcer, but there was no response to the ordinary treatment. There was gastric hypoacidity or anacidity in 42 patients, and occult blood in 12. Radiologically, there was evidence of increased persistalsis and tendency to spasm. Gastroscopy revealed shallow ulcers with irregular edges and smooth pink bases. The mucosa in the area surrounding the ulcer appeared hyperaemic; the folds were not so broad and were less stiff; oedema, such as surrounds the simple peptic ulcer, was not observed in these cases. Erosions were often seen at the lesser curve, and occasionally were the source of profuse haemorrhage. Treatment with arsphenamine produced considerable improvement, even after 1·5 to 2 g. had been given. Increased acidity was a striking feature. In 3 patients treatment had to be interrupted when a profuse haemorrhage necessitated operation. The ulcers were situated in the antrum in all 3 cases; they were shallow and had a hard smooth base and irregular edges. Surrounding the ulcers were several erosions which had previously been detected by gastroscopy. Histologically the submucosa was thickened by granulation tissue, and the infiltration spread both into the muscularis and the mucosa. There were numerous lymphocytes and plasma cells in the perivascular spaces, and the vessels, particularly the veins, showed marked thickening of the intima. Apart from these 3 patients, no evidence of ulcer was present radiologically or gastroscopically after the conclusion of the specific treatment. *Vilma Samet*

2180. **The Occurrence of Gastric Neoplasms in Youth**
M. BLOCK, A. H. GRIEP, and H. M. POLLARD. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 398–404, April, 1948. 6 figs., 6 refs.

At the University of Michigan Hospital 1,913 cases of gastric neoplasm were seen between 1925 and 1945. Of 73 patients below the age of 31 with gastric lesions 50 had benign ulcer, 2 lymphoblastoma, 1 a syphilitic lesion, and 20 carcinoma. The youngest patient with carcinoma was aged 16; 5 patients had free acid in the test meal. Of the 20 with carcinoma pain not quite typical of ulcer was present in 17, and 5 had haematemeses, in 3 cases as the first symptom. In 9 cases a mass was felt and in 17 metastases were present; 16 patients had lost weight and 10 were anaemic. The delay in diagnosis after onset of symptoms averaged 11·4 months, and the duration of life 17·4 months. It is concluded that gastric lesions are rare below the age of 31, but that when one is found there is a 3 to 10 chance that it is malignant. [This is an important observation; Joll's experience led him to the same conclusion.] *W. A. Bourne*

2181. **On the Effect of Some Common Gastric Drugs on the Motility of the Stomach.** [In English]
P. BRUMMER and A. BUNDUL. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 559–574, 1948. 20 refs.

The authors believe that gastric distress is frequently due to disturbed motility of the stomach. They record their observations on the radiological appearances in 137 patients before and after the administration of various drugs by mouth. Atropine sulphate 0·5 g. diminished peristalsis in 27 out of 40 patients but had no effect on tone. Papaverine hydrochloride in 0·1 g. doses diminished peristalsis and tone in the duodenal bulb so that the contents of the latter returned to the stomach when pressure was applied at the time of examination. Sodium bicarbonate (10 out of 10 cases) and sodium barbitone (22 out of 41 cases) increased peristalsis. Calcium carbonate appeared to have no effect in the presence of achlorhydria. Hydrochloric acid, magnesium carbonate, and magnesium oxide exert a greater effect on duodenal motility. The relief which these drugs afford in gastric disturbance is due to their action on motility and not to a chemical neutralization.
E. T. Ruston

2182. **Carcinoma in Chronic Gastric Ulcer: Results of Pathological Examination of 1,720 Resected Stomachs.** (Über das Carcinom im chronischen Magengeschwür. Ergebnisse der pathologisch-histologischen Untersuchungen an 1720 resezierten Magen)
M. HOFFMANN. *Archiv für Klinische Chirurgie* [*Arch. klin. Chir.*] **260**, 570–578, March 31, 1948. 1 fig., 15 refs.

The author analysed 1,720 specimens of resected stomachs in order to obtain an idea of the frequency of malignant changes in chronic simple gastric ulcers. He applied the strict criteria of Hauser to his material. A lesion is considered to have been primarily a simple ulcer if it is round or oval, and has a sharply defined margin and a funnel shape with radiating folds. Microscopically there must be a rolled edge, with scarring at the base. The carcinomatous changes should be confined to the

margin. In addition the author stresses the importance of a long clinical history.

When these standards were applied 62 cases of ulcer-cancer were found. These constituted 6·6% of the 941 ulcers and 8% of the 779 carcinomata. There were a further 34 likely cases, but as these did not strictly comply with all the rules they were not included. The author therefore regards his values as the lowest possible for his series. Of the 62 cases 39 occurred in men and 23 in women: 27 were solid carcinomata, 25 adenocarcinomata, 5 were mixed, and 5 unclassified. The author quotes several other opinions on this subject from the German literature. Some authors deny the occurrence of malignant changes in simple ulcers altogether. This the author attributes to the small number of cases analysed by them. While refuting the idea that simple gastric ulcer is a pre-cancerous condition the author looks upon it as fertile ground for the development of malignant changes in a stomach with a carcinomatous diathesis.

R. Schneider

2183. **Reflux of Biliary, Pancreatic and Duodenal Secretions in Gastric Physiology and Pathology.** (Le reflux des sécrétions alcalines duodéno-pancréatico-biliaires en physio-pathologie gastrique)

A. LAMBLING and J. R. GOSSET. *Archives des Maladies de l'Appareil Digestif* [*Arch. Mal. Appar. dig.*] **37**, 165–180, March–April, 1948. 16 figs., 20 refs.

The authors examined the effect of duodenal regurgitation on the histamine test. After the resting juice had been aspirated and another specimen taken, representing the response to the stimulus of introducing the tube, 0·5 mg. of histamine was injected. During the first hour specimens were withdrawn every 15 minutes, and during the second hour every 20 minutes. Regurgitation was independent of any nausea experienced during the test, and independent of the nature of the stimulating agent. Repeated tests are necessary before any pathological significance is attributed to abnormal findings.

So far as the physico-chemical effects are concerned, there are three possibilities: (1) The total acid curve is little altered, but the free acid curve remains low. The excessive difference between the two curves indicates the introduction of buffer substances by the reflux. This increase may be three to four times the normal. (2) Regurgitation occurs with a sudden drop both in total and free acidity. There is a rapid return to the previous level after the regurgitation has subsided. A moderate increase in buffer substances may also occur in such cases. (3) The regurgitation does not seem to modify the acid curve materially. Some specimens are discoloured. The findings are inconsistent. A slight increase in buffer substances may occur.

The explanation of the first type is obvious. The explanation of the third type is also simple. The authors suggest that in such cases the regurgitant fluid is rich in pigment, but too weak in buffer substances to cause a significant change. The interesting type is the second one. The authors put forward the theory that here some constituent of the duodenal juice causes superficial irritation of the gastric mucosa, and that this irritation by means of a nervous reflex inhibits the function of the glandular cells. Such irritating factors might be the bile salts, trypsin, or the alkalinity of the regurgitating fluid. The authors, however, do not think that such a mechanism in itself is a complete explanation. In addition they assume a sensitization of the gastric mucosa to the duodenal content. In favour of such an assumption is the fact that in patients who have responded to treatment a recurrence of regurgitation will alter the gastric chemistry only after a time interval of several months. As an alternative theory the authors suggest that the reflux might be coincident with the formation of large quantities of enterogastrone. However, the rapidity with which the changes occur is more suggestive of a nervous reflex than that of an endocrine mechanism.

Apart from these immediate effects there is a late one. The reflux in due course leads to a chronic gastritis with progressive diminution of gastric acidity and eventually to complete achlorhydria. Clinically, there is a latent type which seems to occur frequently in diabetics, and a manifest type in which symptoms and chemical changes run parallel and fluctuating courses. According to the authors the cause of the reflux is a duodeno-pyloric dystonia often secondary to intestinal disease such as chronic appendicitis, colitis, or common constipation. It may also have a purely neuro-vegetative origin and occurs frequently in the emotionally unstable. Here it represents the mechanism by which a purely nervous dyspepsia may produce organic changes. *R. Schneider*

2184. **The Bones in Chronic Diarrhoea.** (Lé trophisme osseux dans les états diarrhéiques chroniques)

C. B. UDAONDO and M. R. CASTEX. *Archives des Maladies de l'Appareil Digestif* [*Arch. Mal. Appar. dig.*] **37**, 181–183, March–April, 1948.

The authors have investigated the bones in 40 cases of diarrhoea of various origin. The list of primary diseases includes thyrotoxicosis, amoebic colitis, steatorrhoea, chronic entero-colitis, irritable colon, chronic ulcerative colitis, and tuberculous entero-colitis. Decalcification was frequently found in both sexes, and was present in 82% of the cases studied. [As regards the influence of age, there are several contradictory statements which make it difficult to judge the authors' opinion.] No correlation was found between either the nature of the primary disease or the duration of the diarrhoea and the degree of halisteresis. In 28 patients the blood levels of calcium, inorganic phosphorus, and alkaline phosphatase were estimated; in 3 cases there were no changes. The remaining 25 cases were classified under 4 headings: (1) osteomalacia and rickets; (2) primary nutritional deficiency; (3) hyperparathyroidism; (4) thyrotoxicosis, liver disease, and chronic leukaemias. The authors are of the opinion that the intestinal disease is the primary factor which initiates the changes of metabolism, and in consequence also of bone formation, but that the constitutional abnormality, or, as they call it, the paratype of the individual determines the type of metabolic change.

R. Schneider

2185. **Some Peculiarities of the Clinical Course of Acute Dysentery.** (Некоторые особенности клинического течения острой дизентерии)
V. V. Stavskaya, Z. I. Sosnovic, and B. N. Popov. Клиническая Медицина [*Klin. Med.*] **26**, No. 2, 51–58, 1948.

During the last 10 years dysentery has become less severe and less fatal. Investigations were made on patients in Leningrad in 1943–5. All the patients were examined according to the same plan. Great attention was paid to the macroscopic appearance of the stool. Bacterial examinations were carried out at least 3 times in each case. Most patients had a proctoscopy on the fifteenth to twentieth day. Altogether 548 patients, aged 21 to 45, were investigated. Women predominated, but this may be due to a reduction in male population during the war. In 1943, 56·8% of patients suffering with dysentery had been immunized in that year. Most of the patients were treated in hospital. The ambulatory patients were treated by bacteriophage and sulphonamides. In 1943, the general state of nutrition was very low. Five patients suffered from alimentary dystrophy of second or third degree. In 1944–5 the general condition was much better. Results of bacteriological examinations are shown below.

Year	No. of Patients	No. of Bacteriologically Proved Cases	Types in Percentages					
			Shiga	Flexner	Schmitz	New Types	Sonne	Newcastle
1943	128	58 (45·3%)	—	36·3	24·1	39·6	—	—
1944	289	188 (65%)	6·6	31·6	23·8	25·8	4·8	7·4
1945	131	77 (58·8%)	2·6	32·4	13·0	9·2	31·1	11·7

The 1943–5 epidemic was not very severe, only 47 (7·7%) patients were seriously ill; 92·4% had fever. In 64·8% of cases the number of stools did not exceed 3 a day; only in 0·9% did it reach 13 to 18 a day. The stool in most cases remained faecal; mucus was present in all cases and blood in 69·2% of patients.

In most cases the condition was a left-sided colitis. Only 29·9% of patients had involvement of the whole large intestine. Of the 41·5% of patients who underwent proctoscopy a third had ulcers and erosions, 37·5% had inflammation of the mucous membrane of the large intestine, and 4·1% had a fibrinous or muco-purulent exudate. On the eighteenth to twentieth day, in 16·9% of patients no changes were seen in the mucous membrane of the large intestine.

The general symptoms in the different forms of dysentery were more or less the same; Flexner and Schmitz infections being more severe. In 1943 there were 4 deaths; in 1944–5 there were none. In 1943 the disease lasted much longer, probably because of lower resistance and poorer nutrition. In 1945 only 2 patients had complications, as against 15 in 1943. Three developed a " toxic poliomyelitis " (Venderovich, 1942), and died. In 12 elderly women a disturbance of intestinal motor function, resembling partial obstruction, developed and 1 died. In pre-war days, dyschezia was unknown in connection with dysentery. In 1943 it appeared in patients suffering from alimentary dystrophy, which caused changes in the whole organism and its reaction to the dysentery infection. Very probably it was also the cause of the poliomyelitis. *T. Guercken*

2186. **The Blood and Bone Marrow in the Sprue Syndrome. A Study of 63 Cases**
E. M. Innes. *Edinburgh Medical Journal* [*Edinb. med. J.*] **55**, 282–292, May, 1948. 19 refs.

Previous work on the haematology of the sprue syndrome is briefly reviewed. The author then reports her own observations in 17 patients with tropical sprue, 27 with idiopathic steatorrhoea, and 19 children with coeliac disease. Of the 17 patients who had tropical sprue more than half were receiving enough liver extract to keep pernicious anaemia in remission; in spite of this, macrocytosis was present in 13 out of 16 cases. However, severe anaemia was rare, and this may have been associated with liver treatment. There was no correlation between the type of anaemia and the severity of diarrhoea. In the 27 patients with idiopathic (non-tropical) steatorrhoea the incidence of anaemia was higher and the degree more severe than in the patients with tropical sprue, and again macrocytosis was the rule. In many cases there were considerable numbers of target cells; these do not appear to have been found in the tropical cases. In this group also macrocytosis was often present although liver extract was being given. In coeliac disease, by contrast, the anaemia was typically hypochromic and microcytic; it was refractory to iron by the mouth, although in 1 patient the response to iron given intravenously was excellent. Target cells were often seen. Besides the difference in the type of anaemia, the sex incidence, the author suggests, does not support the theory that coeliac disease is a precursor of idiopathic steatorrhoea in adult life; in the author's series, coeliac disease was more common in females, idiopathic steatorrhoea in males. [It should be mentioned, however, that larger series of cases of idiopathic steatorrhoea do not show a similar preponderance of male patients.] Sternal marrow smears in 18 of the adult patients were mainly megaloblastic, or " intermediate ", in type, but normoblastic marrow was recorded in 4 patients. In 2 of the children with coeliac disease the marrow was actively normoblastic; no other sternal punctures were carried out in this group.

The failure of liver treatment completely to control the anaemia is stressed; in some cases folic acid has improved a liver-refractory anaemia, in other cases not. The most urgent problems remaining to be solved are defined as: (1) the nature of the factor required for the complete restoration of normal erythropoiesis in cases of sprue partially refractory to liver extract and to folic acid, and (2) the mechanism underlying the failure of the hypochromic anaemia of coeliac disease to respond to iron. *D. A. K. Black*

2187. **Studies of Urinary Excretion of Methionine by Normals and by Patients having Liver Disease**
J. E. WHEELER and P. GYÖRGY. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 267–272, March, 1948. 1 fig., 11 refs.

The urinary excretion of methionine was estimated after a single large test dose in patients with proved liver damage and in normal controls. The abnormal group included 4 adults, 3 of whom had portal cirrhosis and 1 toxic hepatitis, and 7 children with the diagnosis of virus hepatitis. Controls of similar age and weight were kept on comparable diets. *dl*-Methionine was given in tablet form to the adults, and in aqueous solution to the children. A single large dose of 5 g. was given to the adults, and 3 g. to the children. The urine was collected for 24 hours before, and for 3 succeeding periods of 24 hours after, the test dose. Methionine was estimated in the urine by the microbiologic assay method of Dunn [for details of which the original should be consulted]. A transient rise in the urinary excretion of methionine occurred in the first 24 hours, but the total amount excreted represented only approximately 10% of the dose given.

The only difference noted between the patients with liver damage and the controls was a slight prolongation of the high methionine levels in the adults suffering from moderately severe hepatic disease. It thus appears that methionine is well utilized by patients with mild or moderately severe hepatic disease. *K. Black*

2188. **Variations in the Serum Proteins in Liver Diseases with Special Reference to their Diagnostic Significance.** [In English]
H. A. SALVESEN and O. LÖDÖEN. *Acta Medicá Scandinavica* [*Acta med. scand.*] **130**, 525–558, 1948. 23 refs.

A detailed analysis is given of the results of blood examination in 148 cases of disease of the liver or biliary tract. The investigations included estimation of total protein, albumin, globulin, albumin–globulin ratio, icterus index, Takata and formol gel reactions, erythrocyte sedimentation rate, and phosphatase. The results illustrate the value of the finding of a low albumin–globulin ratio (below 0·8) in the differential diagnosis of a long-standing jaundice. A fall in this ratio is a better indication of liver damage than the result of the Takata test, and is progressive with the development of cirrhosis.
E. T. Ruston

2189. **On the Significance of Ascites in the Prognosis of Liver Cirrhosis.** [In English]
M. HIRVONEN. *Annales Medicinae Internae Fenniae* [*Ann. Med. intern. fenn.*] **37**, 37–48, 1948. 10 refs.

This study is based on 15 cases of cirrhosis of liver complicated by ascites; 4 patients were discharged from hospital in an improved condition, but in 2 of them ascites continued.

These and a number of similar cases collected from the literature indicate that the prognosis in liver cirrhosis—irrespective of the aetiology—must not be considered poor even if the patient has ascites. No definite conclusions can, however, be drawn from the author's cases as the follow-up period was too short. *H. Herlinger*

2190. **Pancreatic Calculi**
D. COURT and N. M. MATHESON. *Gastroenterology* [*Gastroenterology*] **10**, 848–858, May, 1948. 7 figs., 15 refs.

Three cases of pancreatic calculi are reported from the Ashford County Hospital, Middlesex, England. Altogether some 250 such cases have been reported to date. The authors discuss the pathology, symptomatology, and treatment of the condition.

The stones are composed chiefly of calcium carbonate and tribasic calcium phosphate. Usually there are multiple discrete stones in the larger ducts, but in a few cases a diffuse parenchymatous calcinosis occurs. The cause of this condition, which is almost certainly the result of an antecedent chronic pancreatitis, is obscure. It may develop at any age, but males in the fourth decade are most often attacked. Epigastric pain is the commonest symptom and may be severe. Diabetes occurs in 10 to 40% of cases. Diarrhoea may be present, sometimes with steatorrhoea as well. Hepatic enlargement is an occasional feature, and may perhaps be due to absence of lipocaic. One of the authors' patients had bilateral parotid enlargement, which is interesting in view of the structural similarity between the parotids and the pancreas. The calculi show up clearly in front of the vertebral column when a straight radiograph is taken of the abdomen.

The stones should be removed surgically whenever possible, and cure is probable unless pancreatic damage has been severe and is irreversible. Lipocaic should be given when there is hepatic enlargement, and ephedrine in attacks of pain, for it reduces the volume of pancreatic juice. *John R. Forbes*

2191. **Diagnosis and Present-day Treatment of Pneumococcal Peritonitis.** (Le diagnostic et le traitement actuel de la péritonite pneumococcique)
G. TÖRÖK. *Annales Paediatrici* [*Ann. paediatr., Basel*] **170**, 263–279, May, 1948. 9 refs.

This paper emphasizes the fact that although pneumococcal peritonitis is relatively rare in Britain and the Nordic countries, it was common among the poorer population of Central Europe after the war. All the cases cited occurred in girls, and the possibility of a vaginal portal of entrance is discussed. [The enormous preponderance of females over males would appear to suggest an anatomical explanation.] The clinical picture is well described and the value of estimations of the blood sedimentation rate in doubtful cases is stressed. Penicillin is the treatment of choice, and if this is given early surgery is not usually required. *Patrick Mallam*

[Experimental findings by McCartney (*J. Path. Bact.*, 1923, **26**, 507) showed that the infection was transmitted to the peritoneal cavity by the vagina.—Editor.]

Endocrine Disorders

2192. **The Neutral Steroids of Human Urine: The Significance of the Various Steroid Fractions Excreted in Urine**
S. L. TOMPSETT and E. G. OASTLER. *Glasgow Medical Journal* [*Glasg. med. J.*] **29**, 133–156, May, 1948. 33 refs.

The total daily urinary excretion of the following steroids was estimated in a variety of cases: (1) 17-ketosteroids; (2) free reducing ketosteroids (corticosteroids); (3) pregnanediol; (4) total ketones of the neutral steroids; (5) non-ketones (alcohols) of the neutral steroids; (6) half-succinate esters of the non-ketonic fraction of the neutral steroids.

The cases investigated included 9 normal males, 7 males with various medical abnormalities, 3 normal females, 42 females with various medical abnormalities, and 6 surgical cases. The daily output of total neutral steroids in normal males ranged from 20·4 mg. to 41·2 mg. No significant variation was found in the male medical cases, with the exception of one case of malignant hypertension. In this case the total neutral steroids rose from 16·3 mg. to 30·4 mg. during a severe attack. This rise was mainly confined to the non-ketonic fraction, which rose from 9·3 mg. to 21·3 mg. The daily output of total neutral steroids in the 3 normal females ranged from 15·6 mg. to 33·2 mg. Three cases of Simmonds's disease showed a very low excretion of total neutral steroids (3·8, 3·9, and 5·1 mg.). The 17-ketosteroids were very low. In one case of Cushing's syndrome there was a high total neutral steroid excretion (80 mg.), all fractions being increased. A case of adrenogenital syndrome had a total excretion of 110 mg., but the increase was mainly confined to the 17-ketosteroids. In all the surgical cases there was a rise in total neutral steroid excretion immediately after operation. The non-ketone fraction was mainly responsible for this. The authors also studied 5 women in the ninth month of pregnancy. The ratio of total ketones to 17-ketosteroids was much higher than in most other groups, except the surgical ones. The excretion of 17-ketosteroid was within normal limits, but the total neutral steroids were raised (range 53·6 to 193·2 mg.). It is suggested that the rise in total ketones is mainly due to 20-ketosteroids (pregnanolones) and that the catabolism of progesterone is through these.

A table of formulae and detailed methods of extraction and estimation of various fractions are given in two appendices. *R. Barer*

2193. **Kidney Function in Adrenal Insufficiency**
C. WATERHOUSE and E. H. KEUTMANN. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 372–379, May, 1948. 1 fig., 31 refs.

Nine patients with Addison's disease and 4 with pituitary insufficiency were examined for renal efficiency. The glomerular filtration rate was measured by the mannitol clearance, and the effective renal plasma flow and maximum tubular excretory capacity were determined from the *para*-aminohippuric acid clearance. The rate of glomerular filtration was below normal in all patients at all times. Treatment with testosterone propionate and aqueous adrenal cortical extract caused little if any improvement. The maximum tubular excretory capacity showed marked variations. It was low in all 7 female patients and in the 2 male patients with hypertension, but was normal in the other 4 male patients. Treatment with testosterone propionate, aqueous adrenal cortical extract, or thyroid extract caused no significant change. The effective renal plasma flow was below normal except in 2 patients with severe anaemia in whom it was within the lower range of normal. *A. C. Crooke*

2194. **The Parathyroid: A Study Based, in Part, on Sixty Post-mortem Examinations with Presentation of a Case of Hyperfunctioning Adenoma**
H. U. STEPHENSON and W. L. MCNAMARA. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **215**, 381–397, April, 1948. 17 figs., 46 refs.

A review of the functions, dysfunctions, embryology, and anatomy of the parathyroid glands is accompanied by reports on the glands at necropsy in 60 apparently unselected cases, and a description of a case of osteitis fibrosa cystica. The inferior glands, which have to travel further caudally than the superior in development, are more variable in position. The colour varies from pink, through putty-tan, to greyish-yellow or brown, and does not always suffice to distinguish the gland from thyroid, lymphatic, fatty, or thymic tissue. Histologically, cords or masses of cells are comprised mainly of chief cells with scanty eosinophilic cytoplasm, which may occasionally be completely absent in the " water-clear " cells, more sharply outlined and larger than the chief cells. Islands of oxyphil cells with uniform reddish-pink cytoplasm completely filling them lie usually close to the capsule or stroma. Disease of the glands is divided into primary and secondary dysfunction and neoplasm. Primary hyperplasia has been reported in 26 cases in the literature since 1934, due in each case to uniform transformation of cells into the water-clear type. Primary atrophy is equally uncommon. Secondary change follows chronic renal insufficiency with phosphate retention, or pathological diminution of calcium in the bones from various causes, or trauma. By 1946, reports of neoplasms numbered 337. One gland is usually involved (two glands in 8%) and chief-cell adenomata are frequent. Malignant change is rare. The effects of hyperparathyroidism—changes in the blood (diminished neuromuscular activity), urinary tract (increased loss of calcium, phosphorus, and fluid with calcium deposition), and skeleton—may have existed for years before the diagnosis is usually made. Any benign giant-cell tumour

of bone may indicate hyperparathyroidism. The essential point in diagnosis is to distinguish primary from secondary overaction, and for this distinction repeated determinations of serum calcium and phosphorus, serum proteins, non-protein nitrogen, carbon dioxide combining power, and serum alkaline phosphatase, if there are bone lesions, are recommended. Differentiation of primary renal insufficiency with compensatory parathyroid overaction from a primary parathyroid lesion with a secondary renal lesion is difficult but important, as the latter is an indication for operation. Four cases are dealt with in detail. In the first there was arthritis deformans [osteo-arthritis] of at least 9 years' standing with renal calculi, damaged kidneys, and osteoporosis; water-clear cells were the only constituents of the one parathyroid gland which was discovered. In 2 other cases there were respectively changes due to carcinomatous invasion and irradiation, and an oxyphil adenoma without evidence of hyperparathyroidism. In the fourth case advanced bone changes and calcification of lungs and kidneys were associated with a parathyroid adenoma composed largely of chief cells with islands of pale oxyphil cells. This patient survived operation for 15 days, the serum calcium level falling, but death occurring from an unexplained cause. *W. A. Bourne*

2195. **X-substances Augmenting the Effect of Testosterone upon Male Sex Accessories of Rats.** [In English] E. DINGEMANSE, J. FREUD, and J. J. POLAK. *Archives Internationales de Pharmacodynamie et de Thérapie* [*Arch. int. Pharmacodyn.*] **76**, 44–62, March, 1948. 13 refs.

In 1935 to 1938, the authors reported on the occurrence of substances in the saponifiable fraction of testicular extracts which augmented the masculinizing properties of androgens. These substances, which they called X-substances, were found to enhance the effect of androgens on the growth of the accessory organs of reproduction of castrated male rats when the saponifiable X-fraction was added to the unsaponifiable steroid fraction. When pure steroids were used this augmenting or X-effect could be obtained only with androgens having a hydroxyl group in the 17 position. Subsequently it was found that the propionic or acetic esters of testosterone had the same augmented action in rats. Yet in this species none of the lower fatty acids when unesterified could replace the X-substance or X-substances in a mixture with testosterone. In other species, however, such as mice, guinea-pigs, and macaque monkeys the X-substance mixture was much less effective than the low fatty acid esters.

From a series of experiments reported in this paper the authors conclude that the X-substances are probably highly unsaturated fatty acids with a molecular weight above 300, higher than that of oleic, linolenic, and palmitic acids. The experiments proved that acid sodium palmitate is not an X-substance as suggested by others. The exact chemical nature of the X-substances is still unknown.

It is suggested that their effect may be due to a delay in absorption from the site of injection or to a physical or chemical combination of the X-substance with the male hormone after the injection. This combination may find an especially favourable medium in the subcutaneous tissues of the rat; the result of this combination may be a greater stability of the active material in body fluids, a greater resistance to inactivation by the liver, an enhanced selectivity for the accessory organs of reproduction on which the male hormones act, or a combination of several of these factors. Testosterone gives this X-effect either when esterified with low fatty acids or when mixed with the X-fraction. X-substances alone are inert.

B. L. Frank

2196. **Serum Cholinesterase and the Sex Glands.** (Cholinestérase sérique et glandes sexuelles)
A. D. HERSCHBERG, E. FROMMEL, and J. PIQUET. *Annales d'Endocrinologie* [*Ann. Endocrinol., Paris*] **9**, 117–130, 1948. 26 refs.

The effect of sex hormones on the activity of serum cholinesterase—that is, pseudo-cholinesterase—*in vitro* in guinea-pigs and in man has been studied. The addition of oestradiol to horse and human serum *in vitro* produced a fall in cholinesterase values. Five to 7 injections of 0·5, 1·0, or 1·5 mg. of testosterone per kilo raised the cholinesterase levels of castrated, but not of intact, male guinea-pigs. Similar injections of oestradiol and progesterone increased the enzyme levels of both intact and castrated female guinea-pigs. Clinical studies on patients in different endocrine states showed that an excess of oestrogens and androgens was associated with a high serum-cholinesterase level and a deficiency with a low enzyme level. However, since the cholinesterase values did not always change after clinical recovery, the values could not be used for diagnostic purposes. The vasodilator action of oestradiol is believed to be due to local overproduction of acetylcholine. The oestrone receptors are indicated by the presence of pseudo-cholinesterase in their tissues and by increased production of acetylcholine.

J. E. Page

2197. **Urinary Elimination of Synthetic Oestrogens and Stilboestrol Glucuronide in Animals**
A. E. W. SMITH and P. C. WILLIAMS. *Biochemical Journal* [*Biochem. J.*] **42**, 253–257, 1948. 8 refs.

Clinical experience has shown that oestrogen treatment of carcinoma of the prostate fails after a varying lapse of time in some cases, and this suggests the possibility that continued administration may result in some bodily adaptation, involving an altered metabolism of the drug. Hence it was thought worth while to study the metabolism of synthetic oestrogens in patients and animals. The urinary excretion of oestrogen after the administration of stilboestrol, hexoestrol, dienoestrol, and stilboestrol glucuronide was examined in the rabbit and cat. In the rabbit, about 35% of the administered oestrogen can be accounted for in the urine; in the cat the amount recovered is much less. A possible reason for this difference appeared to be that the rabbit has an alkaline urine whereas that of the cat is strongly acid. However, when rabbits were given a diet that produced an acid urine the results were similar to those obtained in rabbits

on a normal diet. The chief metabolic products excreted by the rabbit are the monoglucuronides, but these substances are metabolized further to inactive products. A striking fact revealed in the experiments is that elimination of high doses of oestrogens is very rapid in spite of the fact that oily solutions were used and the oil remained unabsorbed as long as six weeks later. *Doreen Daley*

2198. **Diabetes Insipidus Due to Sphenoidal Sinusitis. Report of a Case**
K. P. BALL and A. C. THACKRAY. *Lancet* [*Lancet*] **1**, 637–639, April 24, 1948. 2 figs., 6 refs.

A woman, aged 31, previously well, was taken ill with headache, nasal discharge, epistaxis, thirst, and frequency of micturition. When examined 6 weeks later there were bilateral nasal obstruction and middle-ear deafness, and she was passing 9 to 15 litres of urine daily. The Wassermann reaction was negative, and the cerebrospinal fluid was normal, but *x*-ray examination showed pansinusitis. Daily intramuscular injection of 1 ml. of pitressin tannate in oil diminished the urinary output to 3 to 6 litres daily. Antral puncture revealed pus. She died after 18 months with symptoms of nephritis.

Post-mortem examination revealed septic bronchopneumonia and nephritis. All the air sinuses were diseased, and the inflammation in the wall of the sphenoidal sinuses had extended into the pituitary fossa, where the fibrous tissue had caused destruction of most of the posterior lobe of the pituitary gland, which presumably had led to the diabetes insipidus. Only one other similar case has been recorded. *Zachary Cope*

2199. **Experimental Investigation into the Genesis of the Adrenogenital Syndromes by Analysis of the Morphology of the Pituitary in Hyper- and Hypofunction of the Adrenal Cortex in Rats.** [In English]
J. MELLGREN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 284–307, 1948. 12 figs., bibliography.

The author claims that Cushing's syndrome, certain forms of virilism, and Morgagni's syndrome are all manifestations of the adrenogenital syndrome and he suggests that hypertrophy of the prostate is also associated with hyperfunction of the adrenal cortex. He states that all these diseases are characterized by certain histological changes in the anterior lobe of the pituitary gland, notably an increased number of Crooke's hyaline basophil, hypertrophic amphophil, and sparsely granulated basophil cells. These pituitary changes may be associated with hyperplasia, adenoma, or carcinoma of the adrenal cortex. In the present paper he describes experiments designed to show whether the pituitary changes are primary or are secondary to the changes in the adrenal cortex.

Eighteen normal male rats were treated for 30 to 104 days with active corticotrophic hormone. The body weight and the weight of the adrenal glands increased. In the anterior pituitary gland there was pyknosis and probably a reduction in number of basophil cells, a reduction in number of chromophobe cells, and an increase in number of acidophil cells. No hyaline basophil cells were found. This is taken to indicate reduced basophil activity. Thirty other male rats underwent adrenalectomy, and were kept alive for 10 to 86 days with inadequate and decreasing doses of desoxycorticosterone. After about a month the thyroid, prostate, and seminal vesicles were atrophied. The weight of the pituitary gland increased at first and then fell. Histologically, there were an increasing number of hypertrophic amphophil and hyaline basophil cells, some very like Crooke's hyaline basophil cells in the human subject. There was an increased number of chromophobe and a decreased number of total chromophil cells. These changes are taken to indicate an increased production of corticotrophic hormone by the anterior pituitary gland. It is concluded that the pituitary changes found in the adrenogenital syndrome are primary and not secondary to the adrenal changes. *A. C. Crooke*

2200. **Morphological and Functional Comparison of Anti-thyroid Substances.** (Morfologické a funkcionální srovnání některých látek s antithyreoidálním účinem)
H. RAŠKOVÁ. *Časopis Lékařů Českých* [*Čas. Lék. čes.*] **87**, 527–530, April 30, 1948. 2 figs., 10 refs.

Groups of 7 male rats were fed for a period of 24 days with: (*a*) thiouracil; (*b*) 4-methyl-2-thiouracil; (*c*) propylthiouracil, and (*d*) N-methyl-N^1-diethylthiourea. The basal metabolic rate (B.M.R.) was estimated before and at the end of the experiment in a modified apparatus of Junkmann and Hecht. The results showed that the weight of the thyroid gland and the extent of histological changes did not run parallel with the basal metabolic rate in all cases. The period of 24 days was too short to show any marked decrease in the B.M.R. in rats given (*a*) and (*d*), but sufficient to cause a significant fall in rats given (*b*) and (*c*). The values for (*b*) and (*c*) did not differ much. The author recommends methylthiouracil in preference to thiouracil. *J. Ungar*

2201. **On the Biological Activity of Iodinated Proteins and Thiourea.** [In English]
P. FORMIJNE. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 107–115, 1948. 13 refs.

By the iodination of casein thyroxine was formed *in vitro*. To demonstrate this the protein was hydrolysed, the acid-insoluble fraction dissolved in normal sodium hydroxide solution, and the thyroxine fraction isolated with butyl alcohol. Previous addition of thiourea was found to inhibit the formation of thyroxine. Thyroxine was tested both chemically and biologically by its action in the metamorphosis of tadpoles. Iodine added as sodium iodide had no influence on the rate of tadpole metamorphosis. Thiourea does not modify the action of preformed thyroxine, and thiourea in a concentration of 1 in 10,000 caused an increased rate of metamorphosis. *E. F. McCarthy*

See also Section Hygiene and Public Health, Abstract 1947.

Dermatology

2202. **Riboflavin in Skin Diseases.** (Витамин $Б_2$ (рибофлавин) при заболеваниях кожи)
A. V. Drobintseva and A. M. Plotnitskaya. Вестник Венерологии и Дерматологии [*Vestn. Vener. Derm.*] No. 2, 19–24, March–April, 1948. 2 figs.

Little is known of the disturbances of riboflavin and nicotinic acid metabolism in the aetiology of skin diseases. Good results have been obtained in treatment of seborrhoea, sycosis, and streptococcal infections of the skin of the eczematous type with riboflavin. Riboflavin when taken internally undergoes complex changes and acquires the property of penetrating body cells, including those of the epidermis. When this vitamin is deficient, it is well known that the skin respiration and oxidation are lowered and the physiological entity of the skin disturbed. A syndrome consisting of dermatitis, glossitis, and cheilitis occurs, which disappears on treatment with riboflavin. Acne rosacea may be due to ariboflavinosis. Riboflavin is excreted in the urine. It is possible to calculate the amount in the tissues from a 24-hour sample of urine. This was done on a group of patients suffering from various skin diseases and all receiving the same amounts of riboflavin.

Diagnosis	No. of Patients	No. of Tests	Amount Riboflavin in 24-hr. Sample of Urine (μg.)	Variations of Riboflavin in Urine
Lupus	65	240	35	5·2–100
Sycosis	3	9	30	30–34
Eczema	15	45	34	40–59
Seborrhoea ..	10	30	77	36–138
Psoriasis	5	15	93	45–238
Other skin diseases	11	33	100	12–380
Photodermatitis..	5	15	155	113–216
Syphilis	10	20	137	60–264
Total ..	124	407	—	—

The best therapeutic results are obtained in eczema, seborrhoea, and sycosis, and in these diseases the amount of riboflavin excreted in the urine is diminished. The amount excreted in the urine in 24 hours is different after an intake of 12 mg.

Diagnosis	Amount Riboflavin in μg. in Urine on Ordinary Diet	Amount Riboflavin after an Intake of 12 mg.	% Excretion in 24-hr. Sample after Intake of 12 mg.
Lupus	35	1,000	9·0
Eczema.. ..	34	1,037	8·5
Seborrhoea ..	77	1,630	18·0
Psoriasis ..	93	2,625	22·0

It is not the absence of riboflavin from the diet which causes the various skin lesions, but a disturbance of excretion. A hyporiboflavinosis may be a pathogenic factor in the development of skin lesions. A definite relation exists between excretion of riboflavin and the amount of unoxidized products of metabolism. In patients with lupus, there is not only a low content of riboflavin in the urine, but also a lower content of nitrogen and a raised excretion of chlorides. Experiments were carried out to study the effect of increased protein intake on vitamin absorption. Patients with lupus were given 100 g. of casein during 6 days. With casein they were given 46 g. of protein and 500 μg. of riboflavin. On the fifth day, the amount of riboflavin in the urine was increased, this corresponding to an increased intake of riboflavin with casein. On the sixth day, the percentage riboflavin excretion and the nitrogen were determined after an intake of 12 mg. of this vitamin. A sharp change in vitamin excretion was noted, 14% of riboflavin being excreted when 12 mg. of vitamin and no extra protein were given but 36% of the vitamin being excreted when protein was added. This proved that an increase of protein intake causes better absorption of vitamin. During vitamin therapy it is essential to give the patient extra protein. *T. Guercken*

2203. **Dermatologic Evaluation of Yeast, Tyrothricin, Chlorophyll and Nitrofurazone**
H. M. Johnson. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph., Chicago*] **57**, 348–356, March, 1948. 16 refs.

The author inoculated sterile gauze dressings with *Torulospora utilis* var. major. The yeast grew as a whitish mould and permeated the fibres so that the gauze was ready for use in 48 to 72 hours if incubated at 30° C. The gauze was kept moist with 5% dextrose or sucrose solution; it was cut to a convenient size and applied to the skin, the dressings being changed daily. " Scotch tape " (an adhesive plastic tape) and wax paper were used to keep the dressings in place and damp. Six cases of impetigo contagiosa healed under this treatment in 5 to 10 days, 5 cases of ecthyma in 12 days, and 4 cases of infective eczematoid dermatitis in 10 to 15 days. There was only 1 failure in the series, in a case of infective eczematoid dermatitis.

Tyrothricin ointment containing 1 mg. of tyrothricin per g. of base was used for the treatment of 24 patients. The preparation had no value in cases of ecthyma and sycosis vulgaris but was effective for superficial impetiginous lesions.

" Chlorezium " ointment, said to contain water-soluble chlorophyll derivatives, was used to treat 55 patients with pyodermia, ulcers, and contact and atopic eczema. After débridement all lesions were cleansed with detergent soaps before applying the chlorophyll.

The preparation was found to have good possibilities as a topical dressing.

Nitrofurazone (" furacin ") was incorporated in a base consisting of " carbowax " and glycols, and was used in the treatment of 75 patients suffering from pyodermia and allergic diseases of the skin. It was found to be an effective antibacterial preparation and the results closely paralleled those obtained with penicillin ointment.

The author considers that the use of yeast is impracticable and that tyrothricin ointment has little practical value in the treatment of " ordinary diseases " of the skin, but is enthusiastic about " chlorezium " and " furacin ". *R. M. B. MacKenna*

2204. **Myoepithelial Sweat Gland Tumor: Myoepithelioma. Report of Three Cases with a Review of the Literature**
W. F. LEVER. *Archives of Dermatology and Syphilology [Arch. Derm. Syph., Chicago]* **57**, 332–347, March, 1948. 6 figs., 28 refs.

The secretory portions of eccrine and apocrine sweat glands possess an inner layer of secretory cells and an outer layer of myoepithelial cells. Therefore in tumours which affect these portions of the glands secretory and myoepithelial cells are usually found, the former being more numerous than the latter. The author states that there is a group of benign sweat-gland tumours in which the myoepithelial cells represent the majority of the cellular elements. He suggests that they should be called " myoepitheliomata ".

The first section of the paper is concerned with the occurrence of myoepithelial cells in many types of sweat-gland tumour, the second with reports of 12 cases of myoepitheliomata abstracted from the literature of the subject, and the third with details of 3 cases which the author has observed. The paper concludes with a discussion on the classification of apocrine gland tumours. Clinically, myoepitheliomata are usually single, but occasionally multiple, well circumscribed intracutaneous tumours of slow growth. Microscopy reveals epithelial cells arranged in tubules, intertwining bands, or lobular masses. Secretory and myoepithelial cells are present but the latter predominate and are placed, in the epithelial bands, at the periphery and, in the lobules, around and between the groups of secretory cells. Some tumours have much hyaline stroma with areas of mucoid or cartilaginous transformation. They thus resemble the mixed tumours of salivary glands. Most of the lesions are tumours of apocrine origin. *R. M. B. MacKenna*

2205. **Epidermodysplasia verruciformis of Lewandowsky–Lutz.** (Epidermodysplasie verruciforme de Lewandowsky–Lutz)
O. G. COSTA and M. A. JUNQUEIRA. *Annales de Dermatologie et de Syphiligraphie [Ann. Derm. Syph., Paris]* **8**, 131–138, March, 1948. 6 figs., 8 refs.

A case of this rare disease is very fully described. There are good illustrations of clinical and biopsy material. *James Marshall*

2206. **Benign Cutaneous Lymphocytoma.** (Sur le lymphocytome cutané bénin)
K. GAWALOWSKI. *Annales de Dermatologie et de Syphiligraphie [Ann. Derm. Syph., Paris]* **8**, 117–123, March, 1948. 3 figs.

The author describes 3 cases of this rare condition; in 2 the diagnosis was confirmed by biopsy. Treatment was by excision in 1 case and by *x*-ray irradiation in the others. There are 3 theories of pathogenesis: (1) from hypertrophy of islands of lymphadenoid tissue in the skin; (2) from transformation of mesenchymatous cells of the dermis; and (3) from immigration and anaplasia of blood lymphocytes. The following classification is suggested.

(1) *Miliary lymphocytoma:* (1*a*) Agglomerated variety with dark-red follicular papules on the lower limbs. (1*b*) Disseminate variety with small rose or red non-follicular papules of the face.

(2) *Papulo-nodular lymphocytoma:* (2*a*) Disseminated variety with brownish or violaceous lesions of gummatous consistency on the face or, rarely, the arms. (2*b*) Lymphocytoma septi urethro-vaginalis (very rare). (2*c*) Lymphocytoma scroti with red or tomato-coloured lesions on the median raphe of the scrotum in boys. (2*d*) Mammary lymphocytoma. (2*e*) Lymphoma conjunctivae.

(3) *Tuberous lymphocytoma:* (3*a*) Multiple dispersed variety. (3*b*) Solitary variety, lesions having been described on the brow, eyebrow, axilla, epigastrium. (3*c*) Lymphadenosis circumscripta auriculae. (3*d*) Lymphomatosis orbitae. (3*e*) Lymphocytoma of other organs—for example, the parotid gland.
James Marshall

2207. **Vitamin B_2 in Infantile Eczema and Besnier's Prurigo.** (Influence de la vitamin B_2 sur l'eczéma infantile et le prurigo diathésique de Besnier)
R. PÄTIÄLÄ. *Annales de Dermatologie et de Syphiligraphie [Ann. Derm. Syph., Paris]* **8**, 146–148, March, 1948.

The patients studied included 5 with infantile eczema (ages 6 to 12 months) and 21 with Besnier's prurigo (ages 3 to 32 years). Infants were given ½ to 1 ampoule [dose not stated] of riboflavin intramuscularly every other day to a total of 5 ampoules. Others had 2 ampoules of riboflavin intravenously daily (total 25 ampoules) or 1 ampoule of lactoflavine daily (total 10 ampoules). If necessary, a second course was given after a month's rest and a third after 2 to 3 months. Results in infants were more satisfactory in acute than in subacute eczema, but rapid disappearance of itching was a feature. In cases of Besnier's prurigo there was also a good sedative effect, but permanent improvement was obtained in only 2 cases. Subsequent treatment of cases which recurred was never as effective as the original. *James Marshall*

2208. **Erythema Exudativum Multiforme in Childhood**
A. V. NEALE. *Archives of Disease in Childhood [Arch. Dis. Childh.]* **23**, 183–189, Sept., 1948. 4 figs., 39 refs.

Venereal Diseases

2209. **Bismuth Plus Penicillin in the Treatment of Experimental Syphilis**
H. J. MAGNUSON and B. J. ROSENAU. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* [*Amer. J. Syph.*] **32**, 203–211, May, 1948. 14 refs.

"Mapharsen" and penicillin are known to have a synergistic action when combined in the treatment of experimental syphilis. The present article reports experiments which indicate that bismuth and penicillin are similarly synergistic. Rabbits of mixed breeds weighing between 2·5 and 3·5 kg. were inoculated intratesticularly with 10^7 *Treponema pallidum* (Nichols strain). After 6 weeks infection was confirmed by dark-field examination and treatment was started. Six schedules of treatment were followed, including one control schedule in which no bismuth was given. In this last schedule the CD 50 of penicillin alone was 2,650 units per kilo and the CD 90 was 8,000 units per kilo. The addition of one-quarter of the CD 50 of bismuth subsalicylate (1·4 mg. metallic bismuth per kilo) at the beginning of penicillin therapy reduced the CD 50 and CD 90 respectively to 1,000 and 1,800 units per kilo. When the same dose of bismuth subsalicylate was not given until the completion of penicillin therapy so that simultaneous action was prevented, the reduction in the curative dose of penicillin was decreased (CD 50 and CD 90 of 1,500 and 3,300 units per kilo). Conversely, the use of a more soluble bismuth salt at the beginning of penicillin treatment produced a still greater reduction in the curative dose of penicillin (CD 50 and CD 90 of 500 and 1,300 units per kilo). When three-quarters of the CD 50 of bismuth was used even greater reduction in the curative dose of penicillin resulted. Further experiment showed that bismuth did not delay the excretion of penicillin or affect the level of penicillin in the blood, and it was therefore concluded that its action was truly synergistic. Comparing the results of these experiments combining bismuth and penicillin with those of comparable experiments combining mapharsen and penicillin, the authors conclude that bismuth is as effective as mapharsen in supplementing the action of penicillin in experimental syphilis. *S. M. Laird*

2210. **The Treatment of Neurosyphilis with Penicillin**
J. P. MARTIN. *British Medical Journal* [*Brit. med. J.*] **1**, 922–926, May 15, 1948. 12 refs.

The author presents the clinical and pathological effects of penicillin in 24 patients suffering from various forms of neurosyphilis. They were divided into four groups: 8 patients with dementia paralytica, 5 with tabes, 2 with optic atrophy, and 9 with meningo-vascular syphilis. Excluding the tabetic cases and those patients who defaulted, the symptoms in most of the remaining 18 cases were arrested. There were no untoward reactions, no relapses, and no deaths. Usually the Wassermann reaction of the cerebrospinal fluid became negative in 1 year and the number of cells reached normal limits within 2 months. Except for the colloidal-gold reactions and total protein content the cerebrospinal fluid in all cases in the series returned to normal within 12 months. The standard treatment was 5,000,000 units of aqueous penicillin intramuscularly at the rate of 60,000 units every 3 hours. On the first day, however, only 10,000 units was given hourly as a precaution against Herxheimer reactions.

The author concludes that penicillin alone is sufficient therapy in most cases of neurosyphilis, that it can be repeated with advantage after a lapse of several months, and that, with the possible exception of acute general paralysis of the insane, malaria therapy will seldom be called for, and its risks of 8 to 10% mortality seldom be justified. *T. Anwyl-Davies*

2211. **Reactions to Penicillin Therapy for Syphilis**
E. W. THOMAS, S. LANDY, and C. COOPER. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **10**, 77–83, Feb., 1948. 8 refs.

In the authors' experience of the penicillin treatment of over 10,000 cases of syphilis, no serious reactions to the drug were encountered. The complications which were seen are classified as follows:

(1) Urticaria appearing 6 to 12 days after starting treatment, noted in 2·5% of cases treated. Such reactions varied from mild pruritus with a few urticarial lesions to very severe pruritus and marked angioneurotic oedema; in some cases fever was present. Of 804 patients treated for 8 days with penicillin in beeswax and oil, only 2 failed to complete treatment on account of urticarial reaction; in the great majority of cases, including those treated for 18 or 19 days, interruption of treatment was not required, and usually the reactions lasted only for 4 to 6 days whether or not treatment was continued, but in a few cases patients complained of recurrent attacks not associated with further administration of the drug, up to 1 month or 2 months after termination of the course. In 3 cases in which treatment was interrupted at the eighth or ninth day because of severe reactions, injections of the same lot of the drug resumed 10 days later did not provoke a recurrence. Neither "benadryl" nor "pyribenzamine" seemed to influence the onset or course of the urticaria in most cases, although, exceptionally, marked subjective relief was obtained. Intradermal sensitivity reactions with 5,000 units and 20,000 units of penicillin in 0·1 ml. water were uniformly negative, both during and after the injection reactions, in those reacting patients tested [the number is not given].

(2) Exacerbation of secondary syphilitic lesions—a reaction seen only in secondary syphilis, occurring 6 to 10 days from the start of treatment, and lasting for

4 to 10 days, whether or not treatment was continued. The reaction may be associated with local oedema, malaise, sore throat, and high fever, together with the appearances of relapse in the secondary lesions, but in no cases were spirochaetes found on dark-ground examination of serum from such lesions. The authors are unable to classify these phenomena as " delayed Herxheimer reactions " on account of their late onset and protracted course. Their nature is discussed.

(3) Erythematous and papular reactions developing in the first day or two, and lasting for 1 day to 3 days; noted in about 25 cases only. These reactions were always mild and interruption of treatment was unnecessary. The authors believe that such reactions may be associated with fungus sensitivity; the question is discussed in the light of other published cases. (4) Local dermatitis at the site of injection, symptomless and unimportant, though a marked eruption of papules or follicular papules was seen on rare occasions. This reaction appeared on the third or fourth day of treatment. (5) Bullous dermatitis in 2 cases in which bullae appeared on the exposed surfaces of the upper limb.

G. I. C. Ingram

2212. **Destructive Changes in the Cranium in Congenital Syphilis in Early Infancy.** (Alterazioni craniche a tipo destruente nella lue congenita della prima infanzia)
R. BULGARELLI and E. DE MAESTRI. *Policlinico Infantile* [*Policlin. infant.*] **16**, 149–163, April, 1948. 10 figs., bibliography

From the Departments of Radiology and Paediatrics of Genoa University the authors report on 5 cases of defects of the cranial bones in infancy, demonstrated by radiological examination of the skull, and caused by congenital syphilis. The 5 cases came from a series of 13 syphilitic infants observed in 5 months. The patients studied were between 5 and 10 weeks old. In all cases the Wassermann reaction was positive, both in mother and child, and all infants except one, born prematurely, showed in addition osteochondritic and periostitic lesions of the long bones. The defects in the skull were multiple and variable in size, some of them being clearly defined and others more indefinite, involving in all cases the outer as well as the inner table, except in the case of the premature baby in whom the inner table only was involved. There was radiological evidence of periostitis of the cranial bones. The skull defects seemed to respond to antisyphilitic treatment. It was possible to give a full course of treatment in one case only, and in this patient the lesions disappeared completely.

The authors state that the literature on the subject of cranial lesions in early congenital syphilis is very scanty and that such lesions are, on the whole, considered to be very infrequent, an opinion which is contrary to their experience. For the pathogenesis of the lesions described they suggest a multiple origin: an aspecific nutritional disturbance; a fibrous rarefying osteitis as described in the long bones and in other flat bones by Pick; a microgummatous process; and, finally, a true gummatous lesion. The authors think that their findings confirm the opinion of those workers who suggest that there is no hard and fast line dividing congenital syphilitic lesions of early infancy from lesions occurring in somewhat older children. They think that late congenital lesions are quite different from the tertiary lesions of acquired syphilis.

P. E. Polani

2213. **Rapid Treatment of Early Syphilis: Progress Report December 1947**
J. R. HELLER, R. W. BOWMAN, and E. V. PRICE. *Journal of Venereal Disease Information* [*J. vener. Dis. Inform.*] **29**, 103–106, April, 1948.

The results of penicillin therapy at 12 to 15 months in previously untreated cases of secondary syphilis are presented. The authors used 22 different treatment schedules. The numbers of cases actually followed up over this time vary very markedly, and the assumption is made that the experiences of the patients who default are similar to the experiences of those who do not. With penicillin alone, 1,200,000 to 2,800,000 units being given in doses of 20,000 to 80,000 units every 2 to 6 hours, the cumulative failure rates at 12 to 15 months in approximately 1,500 cases varied between 19·1 and 25·4%. In 61 patients given 40,000 units every 2 hours to 3,400,000 units the failure rate was only 4·3%. With penicillin in oil–beeswax the failure rates in 199 patients receiving 8 single daily injections to a total of 4,800,000 units and in 86 patients receiving the same total amount in 16 injections given twice daily were 16·5 and 11·4% respectively. If 300 to 320 mg. of arsenoxide was administered concurrently with 1,200,000 units of penicillin over 8 to 10 days the failure rate in 773 patients was 15·6 to 16·9%. The addition of bismuth did not improve these figures even if the dose of penicillin was increased to 2,800,000 units. Even if three sessions of fever of 3 hours' duration above 106° F. (41·1° C.) were combined with 2,400,000 units of penicillin over 7½ days, the cumulative failure rate was 14·7% in 57 cases. If 1,200,000 or 2,400,000 units were given over 28 to 30 hours with 6 hours of fever the failure rate in 135 cases varied between 25·8 and 35·6%.

Severe reactions were observed in 206 of 32,719 cases treated with aqueous penicillin alone and in 34 out of 11,015 receiving oil–beeswax preparations; there were no deaths in either group. Of 88,202 patients receiving aqueous penicillin and arsenoxide no fewer than 1,402 had severe reactions and 15 died.

R. R. Willcox

2214. **Penicillin Therapy of Late Congenital Syphilis**
R. V. PLATOU and J. T. KOMETANI. *Pediatrics* [*Pediatrics*] **1**, 601–616, May, 1948. 1 fig., 15 refs.

This report concerns the results of treatment of 109 children between the ages of 2 and 13 years suffering from late congenital syphilis; 81 had clinical signs and symptoms; 28 were asymptomatic. Serological tests were carried out in all cases by complement-fixation and flocculation techniques. The most frequent manifestations attributed to syphilis were: abnormalities in the cerebrospinal fluid (36%), lymphadenopathy (35%), clinical neurological signs (18%), enlarged liver (15%), and bony changes (13%). Treatment was with sodium

penicillin, given on the same lines as those recommended for cases of infantile congenital syphilis, namely, a course of 2-hourly or 3-hourly injections for 7 to 14 days in a dosage varying from 10,000 to 50,000 units per pound (0·45 g.). The authors finally recommended at least 50,000 units per pound.

There were no deaths. Benign febrile reactions occurred in 39%. The authors classified their results as clinically satisfactory in 81·6%, uncertain in 9·2%, and unsatisfactory (either no change or actual progression) in 9·2%. Of 98 children who were followed up for 60 days or longer, 52 were under 6 years of age and 46 over 6 years. In the first group either the serum reaction became negative or the titre declined in 84·6%; in the second group only 58·7% showed such changes. Actual dosage of penicillin caused no significant difference, but in those who had received no previous antisyphilitic treatment the results were much better than in those previously treated (and who might be considered particularly resistant). There were 37 such cases; in 27 treatment had been with the heavy metals and was judged inadequate in 24; in 10 penicillin had been given in adequate dosage. Of the 28 asymptomatic patients, 8 became serum-negative, the sera of 15 had progressively declining titres, and 6 were "fast". Improvement in the 20 neurological cases was disappointing. There were 8 cases of condylomata, which resolved within a fortnight; 6 cases of interstitial keratitis, 3 of which did well; 11 cases of malnutrition and anaemia, all of which improved, and 2 cases of Clutton's joints which were cured. In addition a palatal perforation and a gumma responded well. *W. F. Gaisford*

2215. **The Antibody Response in Rabbits to Killed Suspensions of Pathogenic *T. pallidum***

H. EAGLE and R. FLEISCHMAN. *Journal of Experimental Medicine* [*J. exp. Med.*] **87**, 369–384, May 1, 1948. 1 fig., 17 refs.

Syphilitic rabbits, cured after having had the disease 3 months, are usually resistant to infection. The authors carried out a series of experiments to see whether the injection of killed *Treponema pallidum* would protect rabbits against infection. They injected varying numbers of dead pathogenic spirochaetes, obtained by mincing testicular chancres, intradermally, intradermally and intraperitoneally, and intravenously, and found that these rabbits developed positive Wassermann and flocculation reactions, but no immunity against ordinary experimental infection. In the normal controls titres in serum averaged less than 1 in 2; in the experimental animals they were as high as 1 in 96, this antibody response reaching a maximum in 2 to 3 weeks and then remaining constant or falling. When cultured spirochaetes (Reiter strain) were employed no rise in titre was noted. That the antibody was not due to the extract of testicular tissue is shown by the fact that control animals injected with this, with or without Reiter spirochaetes, did not show an increase of titres. It was found that suspensions of organisms containing relatively small amounts of tissue extractives were just as antigenic as those containing large amounts. Antisera from the experimental rabbits did not agglutinate pathogenic *T. pallidum*, did not give specific complement fixation with spirochaetal antigens, and failed to render spirochaetes non-infective. It is considered that Wassermann reactivity induced by injection of dead spirochaetes and the reagin occurring in syphilitic infection represent an antibody response to *T. pallidum*, spirochaetes and mammalian tissue apparently both containing an immunologically related antigen.

A particularly interesting observation was that some animals injected with organisms in a water-in-oil emulsion may have been sensitized by preceding aqueous injections, since the incubation period was reduced; the relation of this finding to the late manifestations of syphilis, in which relatively few organisms produce a disproportionately large tissue reaction, is clear. *T. E. Osmond*

See also Section Digestive Disorders, Abstract 2179.

2216. **Keratosis Blennorrhagica. A Case Report with a Review of the Literature**

E. W. GAULT and E. I. GAULT. *Indian Medical Gazette* [*Indian med. Gaz.*] **83**, 123–125, March, 1948. 7 refs.

A female Indian child aged 7 years was seen at the hospital at Vellore, South India. She was poorly nourished and had hard, thickened, ridged, and fissured scaly epithelium of both lips and horny knobbly masses on the forehead, palms, soles, elbows, and knees. Hard, horny, secondarily-infected cauliflower-like masses were also present on the buttocks, perineum, and inner thighs, and there were also sordes on the gums. The disease had started about a year before with fever lasting for 8 days, which was followed by the appearance of blisters on both lips. These subsided somewhat, but they, in addition to the blisters which then appeared on the other parts, later developed into the present lesions. At no time was there obvious urethritis, conjunctivitis, or arthritis, though there had been a bilateral aural discharge for 2 years. The blood Kahn reactions in both mother and child were negative, and vulvar smears were negative for gonococci and tinea. No gonococcal complement-fixation test was apparently performed. Biopsy material taken from the heels and buttocks showed marked parakeratosis and acanthosis, and was considered consistent with a diagnosis of keratosis blennorrhagica.

The patient was [rather surprisingly] admitted to a venereal diseases ward, where she was given 16·5 g. of sulphadiazine over 1 week concurrently with 6 fever sessions induced by intravenous T.A.B. vaccine on alternate days. Penicillin, 20,000 units 3-hourly, was given until 1,000,000 units had been administered, after which improvement was evident, though a further course of penicillin combined with fever was given a month later. The lesions were treated with Sitz baths and deep *x* rays (12 treatments in 1 month) followed by starch poultices and penicillin cream. Photographs show the lesions before and after treatment.

[The claim by the authors that this article contains a review of the literature is extravagant. There are only 7 references, of which 5 are to American sources; there are no references to British sources.] *R. R. Willcox*

Genito-Urinary Disorders

2217. **Kidney Complications During Sulphonamide Therapy.** [In English]
A. H. ANDERSEN and I. ANDERSEN. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 259–282, 1948. 3 figs., bibliography.

The authors describe the 10 patients with kidney complications resulting from sulphonamide therapy admitted to the Bispebjerg Hospital, Copenhagen, during a period of 18 months. There were 7 cases of mechanical extrarenal damage; all of these patients recovered. A case of mechanical intrarenal injury was fatal. One patient had 2 attacks of toxic intrarenal injury with a 6-month interval, the second attack being fatal. One patient died of what was presumed to be toxic intrarenal injury. Seven of the patients were females. The latent period from the commencement of therapy to the appearance of symptoms averaged 3 days. The average dose given was 21 g., although in 1 case complications occurred after 5 g. of sulphapyridine. Sulphathiazole had been given in all the other cases. Two patients also received "lucosil" (sulphamethylthiodiazole). Case reports are given of representative cases in each group, with necropsy details in fatal cases.

In mechanical intrarenal injury, the kidney is swollen and oedematous and greyish striae in the pyramids radiate towards the cortex. On section amorphous masses containing numerous round cells are seen in the collecting tubules. There is also hyperaemia of the peripheral cortical zones and some interstitial reaction. In toxic intrarenal injury there is a toxic degeneration of the convoluted tubules (similar to that found in mercuric chloride or carbon tetrachloride poisoning) and interstitial round-cell infiltration.

The importance of adequate fluid intake during sulphonamide treatment is stressed. Treatment of the various types of injury is discussed. Eight cases of mechanical extrarenal injury have been previously reported in the Danish literature and are referred to here.

J. Maclean Smith

2218. **Urine Volume and Total Renal Sodium Excretion during Water Diuresis**
A. J. CRUTCHFIELD. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 28–40, Jan., 1948. 6 figs., 32 refs.

Restriction of sodium intake is advocated in the treatment of congestive heart failure. There is disagreement concerning the optimum water intake during the period of sodium restriction. Diuresis and sodium excretion were observed in 50 patients over 6-hourly periods after the administration of water alone or of water and diuretics. In patients in whom the volume of urine was previously adequate, theoretically, for the excretion of solids there was a decreased sodium excretion during diuresis; the cause of this is obscure. In subjects in whom the urine volume was previously inadequate there was an increase in sodium output, which may be due to the elimination of sodium retained during inadequate urinary flow. There appears to be a range of urinary volume necessary for the maximum excretion of sodium. Water diuresis ceases to exert a therapeutic effect when urine volume reaches a level between 2 and 3 litres in 24 hours. Theophylline, theophylline and ethylene diamine, and mercurophylline caused an increase in the diuresis after water was given, disproportionately favouring the excretion of sodium. This suggests that these substances depress the tubular reabsorption of sodium more than that of water. Urea and glucose have a slight and variable effect on sodium excretion. *E. F. McCarthy*

2219. **The Addis–Shevky Concentration Test.** [In English]
J. ØSTER. *Acta Medica Scandinavica* [*Acta med. scand.*] **129**, 513–523, 1948. 4 figs., 12 refs.

Because of the uncertainty as regards the normal figures at various ages for concentrating ability of the kidneys, and because the figures of Addis and Shevky (1922) on American patients appear to be higher than those obtained in Denmark, the authors measured the concentrating ability of the kidneys by determining the specific gravity of the urine in a concentration test with a hydrometer and with a Mohr–Westphal weight. After breakfast, the patient avoided drinking for 24 hours. Urine was collected in the latter half of this period (from 8 p.m. to 8 a.m.). Results of 200 observations in 177 patients aged from 3 to 72 years showed that the average specific gravity decreased in a regular way from 1029 at the age of 5 to 1025 at the age of 55. Statistical evaluation produced limiting values of normal in children of 1020 to 1037 and in adults of 1017 to 1035, there being no difference between the sexes. *E. G. L. Bywaters*

2220. **Calcium Oxalate Nephrosclerosis with Uraemia.** (Calciumoxalatschrumpfniere mit Uraemie)
W. VISCHER. *Schweizerische Zeitschrift für Pathologie und Bakteriologie* [*Schweiz. Z. Path. Bakt.*] **10**, 286–301, 1947. 2 figs., 53 refs.

The post-mortem findings in the case of an 11-year-old boy, who died of uraemia about 4 months after recovery from diphtheria, are described. The kidneys were small and contracted and contained large crystalline deposits of calcium oxalate. Histologically there were extensive fibroses and round cell infiltrations both in the cortex and medulla with rosette-shaped deposits of calcium oxalate. The glomeruli were also fibrosed but no "crescents" were present. Whether the kidney lesions had developed during or after the diphtheritic infection could not be decided. The subject of oxalate metabolism and its relation to kidney disease is reviewed. *G. Popják*

Locomotor Disorders

2221. **Flocculation Tests in Rheumatoid Arthritis**
T. N. FRASER. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **7**, 83–88, June, 1948. 3 figs., 14 refs.

As the empirical tests of liver function are often positive in rheumatoid arthritis an investigation was undertaken to establish their value in rheumatoid arthritis as aids to prognosis and activity. The colloidal gold and the cephalin-cholesterol tests were carried out in 100 cases of rheumatoid arthritis, 30 cases of osteo-arthritis, and 40 cases of rheumatic fever and fibrositis. The colloidal gold test was positive in 61% of patients with rheumatoid arthritis and in 40% of those with rheumatic fever. The cephalin-cholesterol test was similarly positive in 19 and 15% respectively. Neither test bore any relation to the clinical state or to the administration of gold salts, but the tests did bear some relation to the erythrocyte sedimentation rate, and to the globulin fraction of the serum. *D. P. Nicholson*

2222. **Effects of Artificially Induced Fever on the Circulation in Arthritic Patients**
K. G. WAKIM, F. H. KRUSEN, and E. C. ELKINS. *Archives of Physical Medicine* [*Arch. phys. Med.*] **29**, 274–284, May, 1948. 1 fig., 27 refs.

Various types of hyperaemia may be classified into: (1) Passive, which is induced in the organism by such measures as hot baths, long- and short-wave diathermy, luminous and non-luminous heat cabinets; under these conditions the rise in temperature is not provoked by bodily activity. (2) Active, as induced by the injection of foreign proteins, malarial parasites, or some colloidal substances; in this type the body does make an effort to raise its own temperature and the cells are very active in producing heat. Endogenous fever induced, for instance, by the intravenous injection of typhoid vaccine has four phases: (*a*) prodromal, (*b*) chill, (*c*) flush, and (*d*) defervescence. In the hyperaemia induced by physical means the prodromal and " chill " phases are absent and the " flush " phase develops gradually from the onset. Fever is due to an imbalance of the heat-producing and heat-eliminating mechanisms; a relatively small increase in heat production, if associated with a large reduction of heat loss, can produce very high fever. In the development of fever the mechanism of heat loss is as important as that of heat production.

While definite physiological effects are produced—namely, a substantial increase in leucocytes as well as in blood flow, in the cardiac output, in metabolism, and in the number and size of the capillaries—the mechanism bringing about benefit in arthritis is not clear. General heating of the body is regarded as more efficient than the local application of heat to the diseased joint. It is pointed out that patients suffering from rheumatoid arthritis respond poorly to contrast baths as compared with normal persons. The attenuated blood supply may be due either to disuse of the parts or to vasospastic disturbances, which, according to some observers, are common among patients with rheumatoid arthritis.

In the study of the blood flow in man it is obvious that the methods used must be indirect and the body must be kept intact. Two methods have been employed—namely the plethysmographic and the calorimetric. In the latter the rate of flow is determined from the rate of heat loss in the limb. This method has fewer advocates than the plethysmographic because it is believed to have many disadvantages. The plethysmographic method is fully described. " In principle the amount of blood flowing into the extremity is measured by determining the rate of increase of volume subsequent to the obstruction to venous outflow in the limb. The increase of volume of the limb, which occurs for several seconds after sudden inflation of the collecting cuff, indicates the rate of blood flow into the limb."

Adult patients who were being treated for arthritis were studied during various types of fever treatment—cabinet fever, hot reclining baths, or typhoid vaccine administered intravenously. The blood flow in each subject (left forearm) was determined by means of the compensating plethysmokymograph. Several control determinations of blood flow were made immediately before the patient was sent for the induction of fever. Soon after induction of hyperthermia the blood pressure, oral temperature, and heart rate were again recorded. Within 10 minutes after the induction of fever to about 101° F. (38·3° C.) the patients were prepared as described and the blood flow was determined from the left forearm once every 2½ minutes for a period of 40 minutes. Tables summarize the data in 15 patients in whom a temperature of 101° F, was induced by tub baths at temperatures several degrees above that of the body for a period of about half-an-hour. All showed a definite increase in blood flow. It took several hours before the blood flow gradually returned to normal value. The heart rate increased in every case, but the effects on blood pressure were somewhat variable. The data on the effect of hot humid air show that after the induction of fever a considerable increase in blood flow took place. The changes in blood pressure were again very variable. After intravenous typhoid vaccine the changes in circulation were as follows. During the prodromal phase there was slight cutaneous pallor with reduction of blood flow, which became maximal at the peak of the " chill phase ". Soon after the chill a general flushing of the skin took place and the blood flow increased above the control level; this lasted through the period of defervescence. These prodromal symptoms and chills characterized the fever induced by intravenous typhoid vaccine but were entirely absent when fever was induced by physical methods. *M. B. Ray*

2223. **Agglutination of Hemolytic Streptococci (Group A) in Serum from Patients with Rheumatoid Arthritis.** [In English]
K. KALBAK. *Acta Medica Scandinavica* [*Acta med. scand.*] **130**, 358–370, May 15, 1948. 17 refs.

Streptococcal agglutinins have been reported in 51 to 94% of sera from cases of rheumatoid arthritis by 12 groups of workers; the titre (between 1 in 40 and 1 in 640) was much higher than in streptococcal disease or in control patients. After a tabulated review of these papers, the author describes his own modification of the Dawson and Olmstead technique [for details of which the original must be consulted, since small technical variations lead to surprising discrepancies]. In 93% of 800 control cases there was no agglutination; in 38 cases of haemolytic streptococcal infection there were 100% negative reactions; 90% of 100 patients with rheumatic fever had negative reactions, and reactions in all of 9 cases of subacute bacterial endocarditis were negative.

Of 241 patients with rheumatoid arthritis 78% gave a positive reaction. The remainder included a few typical active cases, as well as a number of atypical ones. The author examines the possibility that this reaction may be a specific reaction against streptococci so attenuated that they cease to produce streptolysin, but concludes finally that it is a non-specific reaction which remains to be explained. *E. G. L. Bywaters*

2224. **Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients with Rheumatoid Arthritis**
H. M. ROSE, C. RAGAN, E. PEARCE, and M. O. LIPMAN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 1–6, May, 1948. 5 refs.

An agglutination test is described which is specific for active rheumatoid arthritis. A 1% saline suspension of sheep erythrocytes is prepared from fresh defibrinated sheep blood by washing the cells 3 times in saline, centrifuging, and resuspending. A similar 1% suspension of erythrocytes sensitized by the addition of anti-sheep rabbit serum is prepared, 2 units of haemolysin being used. The unit is determined in the usual way by serial dilution from 1 in 1,000 to 1 in 10,000 of the serum in saline, the addition to each dilution of an equal quantity of 2% washed sheep red cells and one-fifth volume of 1 in 10 dilution of fresh guinea-pig complement, followed by incubation at 37° C. for 1 hour. With each of these 2 suspensions, 1 plain and 1 sensitized, the patient's fresh serum (inactivated by heating at 56° C. for 30 minutes) is titrated in doubling saline dilutions. After incubation at 37° C. for 1 hour the tubes are left in a refrigerator at 4° C. overnight; the end-point is read immediately after removal from the refrigerator by tapping the tube with the finger and estimating the degree of agglutination. The reciprocal quotient of the agglutination titres of each serum for normal and sensitized cells is called the differential agglutination titre (D.A.T.).

Results in 110 cases are shown in tabular form. In all of 27 cases of active rheumatoid arthritis the D.A.T. was 16 or more; in 8 of 16 cases of inactive rheumatoid arthritis the D.A.T. was over 16; in 2 cases of active Still's disease the titre was 128, and in 1 in remission the titre was 4. The only one of 5 cases of ankylosing spondylitis with peripheral joint involvement was also the only one in which the D.A.T. exceeded 16. In other diseases, including rheumatic fever, infectious mononucleosis, and other forms of arthritis titres were low. Thus the test appears to be specific and related to activity of the disease, but it does not run exactly parallel to the erythrocyte sedimentation rate, to haemolytic streptococcus agglutination, or to collodion-particle agglutination. The active substances appear in the globulin fraction. Complement is not required for this test.

E. G. L. Bywaters

2225. **Rheumatoid Spondylitis. Its Early Diagnosis and Treatment**
S. E. REES, E. A. ALBERS, and G. B. NICHOLS. *Northwest Medicine* [*Northw. Med., Seattle*] **47**, 260–263, April, 1948. 9 refs.

This paper deals with the diagnosis and treatment of 150 cases of ankylosing spondylitis sent to an *x*-ray therapy department. All the patients were civilians and were referred by a single general practitioner over a period of 3 years, 99 being women. *X*-ray therapy was employed in every instance. If the condition was not acute the patients were given small doses by a wide-field technique twice weekly for 6 to 8 weeks. In acute cases localized areas were treated, two larger doses (140 r to each of three regions) being given on alternate days and repeated in 6 weeks. Some 120 patients improved with deep *x* rays, and of these 25 relapsed in 6 months. There was a decrease of 1,000 or more white cells per c.mm. after treatment in three-quarters of the cases. No mention is made of menstrual disorders following radiotherapy.

H. A. Burt

2226. **Vertebral Haemangioma.** (Гемангиомы позвоночника)
V. V. PISHTSHUGIN. Вопросы Нейрохирургии [*Vop. Neirokhir.*] **12**, No. 3, 40–46, May–June, 1948. 1 fig.

The author describes 17 cases of vertebral haemangiomata seen in the last 10 years. He emphasizes their rarity as a clinical finding in comparison with the number discovered at necropsy because in most cases they give rise to no symptoms. He agrees with Makricostas, who states that symptoms most often occur in young subjects.

All of the 17 patients were under 50 years of age. Almost all the haemangiomata were in the dorsal vertebrae; the location was dorsal in 12 cases, dorsal and cervical in 2, and cervical alone in one case. In 2 cases dorsal haemangiomata were associated with similar lesions in the left parietal and frontal bones of the skull. In 12 cases only one vertebra was affected, in 4 cases two adjoining or separate vertebrae were affected, and in 1 case four vertebrae. The duration of symptoms varied widely in the series. In one case paraplegia developed 3 months after the first symptom and in others 7 to 12 years elapsed before compression of the cord occurred.

A more rapid course is usual in young patients. The protein content of the cerebrospinal fluid was increased in 7 cases with an increase in cells in 2 cases. The best response to deep *x*-ray therapy was obtained in the case in which the protein content and the cell count of the cerebrospinal fluid were highest (660 mg. per 100 ml. and 23 cells per c.mm.). Deep *x*-ray therapy was given in 14 out of the 17 cases. There was considerable improvement in 3 cases with the shortest history of symptoms, a moderate improvement in 6 cases, and no response in 3. In the 3 unsuccessful cases there was a history of several years' duration and complete paraplegia. *X*-ray therapy was abandoned in 2 cases because of widespread haemangiomatosis of the skin and bones.

The author concludes as follows: (1) Haemangiomata of the vertebrae are characterized by slow growth and absence of metastases. (2) Compression of the spinal cord is seen most often in young subjects. (3) Vertebral haemangiomata are usually solitary, but occasionally more than one vertebra is involved. (4) The duration of the disease from the primary symptoms to the appearance of clinically pronounced phenomena is from 1½ months to 12 years. (5) The disease usually begins with motor disturbances, more rarely with pain or sensory disturbances. (6) Diagnosis during life may be made from a good radiograph of the spine, but in some cases of spinal compression a diagnosis of haemangioma may be suspected if: (*a*) there are remissions, even though slight, in the course of the symptoms, (*b*) there is tenderness on palpation or tapping over the affected vertebra, (*c*) there is pain in the region of the vertebra on inclining the head forwards. This sign is almost always found and remains even after *x*-ray therapy. It appears to be due to sensitivity of the vertebra to tension on its interspinous ligaments. (7) Deep *x*-ray therapy should be given to all patients with spinal haemangiomata, particularly to those with a short history and slight symptoms. It is possible that young vascular tumour tissue can easily be destroyed by *x* rays. In contrast, in long-standing cases this tissue is more difficult to destroy by *x* rays and the secondary changes in the vertebra and cord are irreversible. (8) In cases of unsuccessful *x*-ray therapy laminectomy and decompression followed by more *x*-ray therapy are necessary.

[This article confirms previously recorded views on the clinical aspects of these tumours but adds nothing new.]

J. MacD. Holmes

2227. **Chronic Idiopathic Hypertrophic Osteo-arthropathy**

J. D. Camp and R. L. Scanlan. *Radiology* [*Radiology*] **50**, 581–594, May, 1948. 7 figs., 31 refs.

Chronic idiopathic hypertrophic osteo-arthropathy is a condition occurring predominantly in males at the age of puberty or adolescence and characterized by the osteo-arthropathic syndrome—clubbing of the digits, enlargement of bones and joints, and thickening of the skin of the face—in the absence of any demonstrable primary disease. Its course is slowly progressive to deformity and disability, which are often of extreme degree. Conditions presenting similar clinical and radiographic features have been called hypertrophic pulmonary osteo-arthropathy, familial acromegaloid osteosis, and acropachydermia and pachyperiostitis.

Chronic idiopathic hypertrophic osteo-arthropathy shows a relation to puberty which suggests a constitutional disease made apparent by the endocrine imbalance of that period. The authors calculate that this form constitutes 3 to 5% of all cases. There is no indication of a primary disease. It appears to begin about puberty, is but slowly progressive, has a familial tendency in 60% of cases, and a seasonal fluctuation. The features become coarse, the nose bulbous, the fingers clubbed. There is hypertrophy of the nipples, feminine distribution of hair, acne vulgaris, and excessive perspiration of the hands, feet, and axillae. The subcutaneous tissue is thickened—a non-pitting oedema. The extremities when dependent are cyanosed, indicating some disturbance of vascular dynamics. The epiphyses, tarsus, and carpus are unaffected. Periosteal accretions are found on all tubular bones except the phalanges, whose terminal tufts are atrophied. The chest, skull, spine, and urinary tract are normal. The condition may begin fairly suddenly at puberty and then progress very slowly over many years, thus differing from the form due to leukaemia, carcinomatosis, and pulmonary disease.

James F. Brailsford

2228. **Social and Nutritional Factors in Adolescent Osteochondritis of the Spine**

F. H. Kemp, D. C. Wilson, and E. Emrys-Roberts. *British Journal of Social Medicine* [*Brit. J. soc. Med.*] **2**, 66–70, April, 1948. 2 figs., 15 refs.

This paper summarizes a series of investigations conducted on the distribution and the hitherto obscure aetiology of juvenile osteochondritis of the spine (Scheuermann's disease), and gives an account of its relation with malnutrition and a possible relation with fluorine.

Two groups of boys were compared; the first group taken from a public school and the second from the poorer quarters of Oxford. The incidence of disturbances of ossification of the spine in the two groups was similar, although none of the boys had severe changes. Some of the boys in the first, and presumably better nourished, group had evidence of dental fluorosis, whereas none in the second group, which was not exposed to a high fluorine intake, was thus affected.

Both these groups were compared with another group of children living in a village community where dental fluorosis affects nearly all the inhabitants and considerable poverty had formerly prevailed. In this group spinal changes occurred more than three times as often as in the other two groups and the disturbances were, in some instances, more severe. In view of the known association of endemic dental and osseous fluorosis with malnutrition in other countries, the possibility of a similar association in the case of dental fluorosis and juvenile osteochondritis in Britain must now be borne in mind.—[From the authors' summary.]

Neurology

2229. **Clinical and Pathological Features of Human Cerebral Necroses due to Irradiation.** (Aspects cliniques et pathologiques des radionécroses cérébrales chez l'homme)

L. VAN BOGAERT and J. HERMANNE. *Annales de Médecine* [*Ann. Méd.*] **49**, 14–44, 1948. 9 figs., 12 refs.

The literature concerning radionecrosis in man is reviewed by the authors with some reference to the experimental production of the same condition in animals. They recognize an early reaction, maximal at the end of 5 weeks and then subsiding, and a late reaction which may develop either shortly after or several years after irradiation.

The present paper is based on the careful observation of 2 cases. The first was in a male child aged 3 years and 3 months suffering from tinea and epilated by *x* rays (5 fields, 3 antero-posterior and 2 lateral, 400 *r* per field, filter 1 mm. aluminium, 8 kV, irradiation on 3 successive days). Three and a half months after irradiation the child returned with radionecrosis of the scalp, generalized muscular hypotonus, and a convergent strabismus. He gradually became apathetic and developed a flaccid hemiplegia on the right side with extensor plantar responses on both sides. Later the hemiplegia became spastic. At this stage lumbar puncture revealed an increase in pressure and in albumin content of the cerebrospinal fluid. Gradually a state of generalized contracture developed, with the head and eyes deviated to the right. In the last week fever (38° C.) was present and the child died after 6 weeks' illness. At necropsy there was superficial congestion of the brain with oedema. The meninges were adherent in the intercerebral sulcus. In the frontal regions small haemorrhages were common. The corpus callosum was oedematous and there was congestion of the cortex at this level. The internal capsule was markedly affected by necrosis. In the section passing through the substantia nigra further haemorrhages and central softening were seen. On histological examination the three essential changes were those of oedema, precipitation of large cotton-wool patches of crusty, grumous, and refractile material, and disseminated pronounced hyaline degeneration of the walls of vessels which was not related to the distribution of the precipitate. The vascular lesion was associated with an adventitial reaction. The precipitated masses in the parenchyma were polycyclic in outline and stained blue to violet with haematoxylin and eosin and yellow with van Gieson, but did not give the staining reactions of amyloid and had certain properties of colloids. They contained some globules of material which had undergone pre-lipoid degeneration and some of which had been taken up by the granular capsules. There was no marked production of reticulin, and vascular thromboses were not found. In the pyramidal tracts there was some early reactionary gliosis.

The second case was in a man of 61 who developed a basal-cell carcinoma of the scalp which was treated by irradiation from 6 radium needles for 5 days. [The details of dosage are not recorded.] Shortly after irradiation, epilation occurred and headaches developed with swelling of the right hemicranium and side of the face (opposite to that irradiated). He was well for 3 years and then developed Jacksonian epilepsy, an attack commencing with shaking of the affected side of the face and spread of tremor to the hemithorax and leaving a residual speech defect which disappeared slowly. Three more attacks occurred during the following 3 months. Tendon reflexes were weak on the right side and an equivocal extensor plantar response was present on the same side. There was a slight rise in the cell and albumin content of spinal fluid. A diagnosis of irradiation cicatrix in the left fronto-parietal region was made. *J. Maclean Smith*

2230. **Histopathological Findings in General Paresis After Penicillin Treatment: Report on 4 Cases**

R. H. F. SMITH and V. DE MORLAIS. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 70–76, Jan., 1948. 24 refs.

No previous reports on the neuropathological findings in paresis after penicillin therapy have appeared. The dosage in the 4 cases reported here ranged from 2,400,000 to 4,800,000 units. In 2 of the cases there was clinical as well as serological improvement; the 2 cases which did not improve were of the juvenile type of general paresis, 1 of them a Lissauer type. Histological examination of the brain of the 2 patients who benefited revealed less intense inflammatory changes than in untreated cases. The iron reaction was positive in all 4 patients, but was less pronounced in the 2 who improved. No spirochaetes were found in any of the brains. These findings resembled those obtained at comparable times after malaria treatment. The possibility that penicillin may produce an initial exacerbation of the process is suggested by the 2 unimproved cases. From the results it would appear that penicillin alone can influence the pathological progress of general paresis. *E. W. Anderson*

2231. **Kernicterus. A Review with a Report of the Findings in a Study of Seven Cases**

P. F. L. BECKER and P. VOGEL. *Journal of Neuropathology and Experimental Neurology* [*J. Neuropath. exp. Neurol.*] **7**, 190–215, April, 1948. Bibliography.

This is the most exhaustive study of the pathology of kernicterus which has yet appeared. The 46 cases in the literature verified by necropsy are analysed with full descriptions of the clinical, anatomical, and histological findings, and a further 7 personal cases are recorded. The authors' cases were all associated with erythroblastosis foetalis. In 5 cases the infants were Rh

positive whilst the mothers were Rh negative with anti-Rh agglutinins. To explain deposition of the pigment in the nerve cells the suggestion is made that substances derived from haemolysis of red blood cells acting in the presence of an immature reticulo-endothelial system may increase the permeability of the haemato-cephalic barrier, and that these substances may change the polarity of the membrane of the nerve cells. This change in polarity of the membrane might then permit penetration by bile pigment. In the authors' cases, deposition of pigment in the nerve cells was present in order of frequency in the hippocampus, the basal ganglia, midbrain, medulla, and floor of the fourth ventricle. Where much pigment was deposited the nerve cells were shrunken, whilst some showed poorly staining cytoplasm and vacuolization. No changes were found in the glia cells, microglia, or connective tissue. Whereas clinical neurological manifestations were reported in most cases in the literature, the authors found them in only one of their cases. Slow choreo-athetoid movements of the limbs were observed in this case. The authors state that the neurological signs described in the literature of kernicterus cannot be regarded as specific.

Ruby O. Stern

2232. **Characters of Acute Neuro-infection, with References to Cases Seen at the Khabarovsk Clinic from 1939–1947.** (Характеристика острых нейроинфекций по материалам хабаровской клиники нервных болезней за 8 лет (1939–1947))
V. M. KANTER. Невропатология и Психиатрия [*Nevropat. Psikhiat.*] **17**, No. 1, 16–20, 1948.

An epidemiological and statistical analysis is given of 409 cases of neuro-infection seen at the Khabarovsk clinic over a period of 8 years. Out of 376 cases of neuro-infection due to different viruses there were 209 cases of tick-borne encephalitis, but no cases of autumnal encephalitis. A detailed clinical analysis will be published at a later date. *H. P. Fox*

2233. **The Clinical Picture of Diffuse Sclerosis of the Frontal White Matter with Cerebellar Cortical Atrophy.** (Über das klinische Bild bei diffuser Stirnhirnmarksklerose mit Kleinhirnrindenatrophie)
K. SIMMA. *Monatsschrift für Psychiatrie und Neurologie* [*Mschr. Psychiat. Neurol.*] **115**, 181–193, March–April, 1948. 5 figs., 21 refs.

This is a detailed clinical and pathological report on a case in which, within 3 years, symptoms developed much resembling Pick's disease. A man of 41, from a healthy family, gradually became apathetic, did not speak spontaneously, and neglected his personal habits. Finally frontal signs appeared with pronounced intellectual dementia. The section of the brain did not reveal the expected picture of a cortical atrophy. Diffuse sclerosis was found in the white matter of the frontal lobes. The frontal cortex was only secondarily affected in the areas where connexions with the thalamic nuclei were severed. There was also a widespread atrophy of the Purkinje cells and ganglion cells in the cerebellar cortex.

Discussing the findings the author expresses the view that the functions of the frontal lobes must not be considered separately but in conjunction with thalamic and lower centres with which the frontal cortex is connected. Any lesion which affects this functional entity may produce a "frontal dementia". Attention is also drawn to the atrophy of the cerebellar cortex hitherto not reported in connexion with diffuse medullary sclerosis. *J. T. Leyberg*

2234. **Electroencephalography with Pharyngeal Electrodes**
J. ROUBICEK and D. HILL. *Brain* [*Brain*] **71**, 77–87, March, 1948. 4 figs., 12 refs.

Electroencephalographic records were taken with a three-channel instrument, single and double pharyngeal electrodes being used as well as scalp electrodes. The electrodes were inserted through the nose. It was not necessary to pierce the mucosa or bone. Twelve subjects were examined; 3 were normal, 3 were epileptic patients, 2 had pituitary tumours, and 4 had psychoses. In the normal subjects with pharyngeal electrodes little alpha rhythm was recorded, and there was no sign of the activity evoked in the occipital region by photic stimulation. The main component was low-voltage beta activity, unaffected by opening and closing the eyes. During wave-and-spike episodes in epileptics the disturbance was usually obvious first in scalp leads, and sometimes simultaneously in scalp and pharyngeal leads, but never first in pharyngeal leads. In the cases of pituitary tumour, theta rhythm of moderate voltage and regularity was recorded from the pharynx, and in 1 case delta activity was also present: neither of these features was visible in scalp leads. The pharyngeal electrode is as near to the mid-brain, pons, medulla, and inferior temporal cortex as to the hypothalamus, and a "unipolar" pharyngeal electrode is as diffuse as any other, but employment of bipolar electrodes in this region may be of real value in detecting early disturbances in the basal structures and cortico-hypothalamic circuits, provided that sufficient amplification is available and artefacts can be avoided. *W. Grey Walter*

2235. **Physiological Mechanisms Underlying the Electrical Activity of the Brain**
M. A. B. BRAZIER. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **11**, 118–133, May, 1948. 11 figs., 56 refs.

The effects of hypoxia were studied in 200 experiments, of hypoglycaemia in a large series, and of "pentothal" anaesthesia in 112 experiments. A three-channel Grass apparatus was used; in the later experiments a Walter automatic electronic analyser replaced the manual methods previously described. Inter-channel phase-discriminating analysis permitted measurement of local changes in electrical activity. During hypoxia without gross changes in consciousness or behaviour, the main alteration in the electroencephalogram (EEG) was a gradual shift of the alpha frequency from 10 to 11 cycles per second (c/s) down to 5 to 6 c/s, at which frequency it was still responsive to visual stimulation. In one

subject who fainted there was a more sudden appearance of theta (4 to 7 c/s) activity associated with autonomic signs, then abrupt appearance of delta (2 to 3·5 c/s) at the moment of fainting. The slowing of the EEG was accompanied by an increase in heart rate. During hypoglycaemia a similar shift in frequencies occurred, first evident at blood-sugar levels between 60 and 70 mg. per 100 ml., but the frequency did not usually fall below 7 c/s. Visual stimuli were still effective. It is suggested that a similar mechanism underlies the action of hypoxia and hypoglycaemia, and that this includes a progressive deceleration of the synchronized beat of a uniform neurone population, which may be a component of a cortico-thalamo-cortical retro-active circuit. The changes in pentothal anaesthesia were more complex; higher frequencies appeared during the first stage, with clouding of consciousness or euphoria. At the moment when consciousness is lost the fast activity is replaced instantaneously by slow rhythms. Some alpha activity is present throughout but is not responsive to visual stimulation. During recovery fast activity returns before the slow rhythms disappear. The origin and significance of these various effects are discussed.

W. Grey Walter

2236. **Spontaneous Subarachnoid Hemorrhage of Aneurysmal Origin. Factors Influencing Prognosis**
W. B. HAMBY. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **136**, 522–528, Feb. 21, 1948. 6 figs., 18 refs.

This paper provides a statistical review of the symptoms, signs, and outcome in 130 cases of spontaneous subarachnoid haemorrhage believed to be due to ruptured aneurysms of the circle of Willis. The cause of bleeding was established at operation or necropsy in 47 cases, and in 41 of these the bleeding was due to aneurysmal rupture. A brief review of the history and literature is followed by an analysis of personal cases. The anterior portion of the circle, fed by the carotid artery, was more often affected than the posterior, and the left side more often than the right. The immediate over-all mortality was 51·5% and did not vary significantly with the patient's age. The death rate was higher in second and subsequent attacks (72%) than in the first attack.

J. St. C. Elkington

2237. **Vasopressor Reactivity in Cerebral Vascular Disease as Measured by the Cold Pressor Reaction**
A. H. BECKER, J. MICHAELS, and C. B. WILBUR. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **107**, 160–166, Feb., 1948. 20 refs.

The purpose of this investigation was to demonstrate the correlation between cerebral vascular disease and the reactivity of vasopressor centres as measured by the cold pressor reaction; 20 patients suffering from cerebral arteriosclerosis and 15 patients with meningo-vascular syphilis were selected. The average age of the combined groups was 59·83 years. Control groups were selected from healthy male subjects and divided into 2 groups with average ages of 53 and 24 years respectively. Patients with signs of anxiety or other complications were not included. In the test, the subject rests in a dark room; a basal level of blood pressure is then determined after several readings. The left hand is then immersed in water at 38° F. (3·3° C.) for 1 minute. Blood pressure is recorded 30 and 60 seconds afterwards. The results showed that with advancing age there is an increased average cold pressor response. An increase also occurred in meningo-vascular syphilis but the greatest reactions were noted in subjects with advanced cerebral arteriosclerosis, particularly when hypertension was present. It would seem likely that when vascular changes have progressed to the extent of affecting higher cortical centres, the vasomotor centres are also either affected by generalized ischaemic changes or released from cortical inhibition. As abnormal reactions were obtained in cases of syphilitic vascular lesions it may be concluded that such abnormality of responses noted in cerebral arteriosclerosis cannot be attributed to other changes present in senility.

A. Limentani

2238. **Transient Cerebral Paralysis in Hypertension and in Cerebral Embolism with Special Reference to the Pathogenesis of Chronic Hypertensive Encephalopathy**
G. W. PICKERING. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **137**, 423–430, May 29, 1948. 2 figs., 38 refs.

The views of Traube and Volhard concerning the mechanism of acute oedema of the brain are contrasted as a pathological basis for the cerebral incidents in acute nephritis, pregnancy toxaemia, and the acute exacerbations of chronic nephritis. Volhard supposed that the cerebral oedema was due to marked constriction of the arterioles with resulting anoxia and capillary damage. [Peabody in 1891 had ascribed the transient paralyses in chronic hypertension to spasm of a cerebral artery.] Because of the thinness of the walls of cerebral arteries, their relative lack of muscle, and their known feeble behaviour experimentally to vasoconstrictors, the hypothesis of local spasm is not one to be adopted if a reasonable alternative exists. Traube's theory is that the oedema is caused by diminished blood proteins and raised arterial pressure, though no clear evidence has been produced to show that plasma proteins play any part. His explanation implies that the cerebral arterioles are relatively feebly constricted by the agent which in hypertension raises the arterial pressure, so that the cerebral capillary pressure is raised; in support of this, quite apart from the weak response of cerebral arterioles to constrictor agents, is the fact that there exists in hypertension a relation between cerebrospinal pressure and the diastolic arterial pressure. In chronic hypertension the attacks are sometimes very brief; nevertheless, Rosenberg's study of the brains in 17 cases of malignant hypertension leaves undecided the problem whether the ischaemia is due to spasmodic or organic arterial obstruction, although in some cases the latter was clearly the cause; in 12 of his cases, for instance, he found multiple microscopic infarcts in the basal ganglia, cortex, white matter, brain stem, and cerebellum.

The author, from a personal study of 11 cases of chronic

hypertensive encephalopathy and a consideration of other published cases, concludes that there is no dividing line between the paralyses of cerebral origin that are transient and those that clear more slowly leaving a residual paralysis, and that both kinds of attack are associated with focal lesions of ischaemic origin in the brain. The speed and completeness of recovery from paralysis depend on the size of the final infarct and on its position. As thrombosis is not always found even in those brains which have been exhaustively studied, spasm as a cause cannot always be excluded. But because of the close resemblance between the cerebral events of chronic hypertensive encephalopathy and those complicating mitral stenosis and auricular fibrillation, several examples of which are quoted, the author concludes that the mechanism is probably the same—namely, obstruction of the arterioles, in the former instance by thrombosis, in the latter, embolism. The two principal factors in recovery would appear to be the opening up of the circulation by the moving on of the clot, possibly into a branch, and the restoration of the circulation through collateral channels. The author reminds us that in 1880 Hughlings Jackson said that " transient paralysis may be owing to a small clot or to softening from blocking of a small vessel ". *W. H. McMenemey*

2239. **The Electroencephalogram in Cerebrovascular Disease**
H. STRAUSS and L. GREENSTEIN. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 395–403, March, 1948. 5 refs.

Electro-encephalographic (EEG) records were taken with 3 channels and an assortment of electrode placements. An elaborate classification of degrees and types of abnormality was employed to assist correlation with clinical features in 95 cases of cerebro-vascular catastrophe. There was some correlation with the state of consciousness. When present, an EEG focus corresponded to the site of a lesion, but often there was no abnormality. In none of 14 cases with convulsions did epileptic EEG patterns appear. Abnormalities are much less frequent than in cases of cerebral tumour, and such as are found tend to diminish rather than to increase with time. *W. Grey Walter*

2240. **Subdural Hematoma: An Experimental Study**
R. COHN. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 360–367, March, 1948. 4 figs., 3 refs.

Records were taken of the electroencephalogram (EEG) in 32 cats, electrodes being screwed into the skull a day or two previously. A 6-channel instrument was used with both unipolar and bipolar connections. The latter usually gave the most precise location of abnormal components. When the animals had recovered from the insertion of the electrodes, control records were taken and 2 to 4 ml. of citrated whole blood was then injected subdurally. Injection in the frontal region tended to increase respiration and pulse rates and decrease alertness at once; later, hemiplegias and gross autonomic disturbances appeared. Injection in the parietal area produced immediate paralysis and blindness. Four animals had convulsive seizures. The EEG disturbances consist of, first, total absence of all potential changes for 1 to 3 minutes, then large slow irregular waves on the contralateral side, with continued quiet on the side of the lesion. Five minutes later in all regions there was often large slow activity, less complex and more rhythmic over the lesion. Ten minutes after the injection, bilateral small activity of higher frequency appeared, sometimes with volleys of spikes over the lesion. From this time on, focal delta waves were located over the lesion, the opposite side returning to normal over a period of weeks. The low-voltage phase is regarded as evidence of " shock ", the presence of slow waves as characteristic of reversible abnormality, persistence of low voltage as evidence of local destruction of nerve tissue, and return to normal patterns as recovery of normal function. These findings are not characteristic of haematoma, but are found with any acute lesion. *W. Grey Walter*

2241. **Congenital Extradural Medullary Cysts and their Relation to Juvenile Kyphosis.** (Les kystes spinaux extraduraux congénitaux et leurs rapports avec la cyphose dorsale juvénile)
L. ROUQUÉS, J. GUILLAUME, C. RIBADEAU-DUMAS, and R. ROGE. *Annales de Médecine* [*Ann. Méd.*] **49**, 369–395, 1948. 6 figs., 29 refs.

The authors report a case of spinal compression in the mid-dorsal region in a youth of 14 which proved to be due to an extradural cyst. The usual symptoms and signs of spinal compression were present including subarachnoid block and expansion of the spinal canal demonstrated by radiological examination. The wall of the cysts was of fibrous tissue. The literature on the subject is reviewed in detail. *J. St. C. Elkington*

2242. **The Epileptic Attack, Sleep, Periodicity.** (Anfall, Schlaf, Periodizität)
K. H. STAUDER. *Nervenarzt* [*Nervenarzt*] **19**, 107–119, March–April, 1948. 45 refs.

Fits precipitated by disturbances of the usual sleep rhythm, especially deprivation of sleep, are described in soldiers on active service. They occurred for the first time in 38, who were all over the usual age for the onset of epilepsy. Fits became more frequent or recurred after a long free interval in 34 epileptics (3 with traumatic epilepsy), the patients showing increased excitability. In many subjects in both groups there were chronic or periodic sleep abnormalities, the most frequent being anxiety, tremors, or muscular twitchings on falling asleep or on awakening. There was marked lability of the rectal temperature in 20 of 26 patients; the daily variation was over 1·5° C., there was disturbance of the normal temperature rhythm, and a marked dependency on external temperature with rapid cooling when exposed to cold. The author compares the sleep abnormalities and temperature variations with the phenomena of hibernation. Sleep and temperature regulation in relation to phylogenesis are discussed, and attention is drawn

to the possibility that the remains of a phylogenetically older thermo-regulating system act occasionally as a disturbing factor. The manifold relationship of the epileptic fit to the sleep rhythm is emphasized by the fact that fits often occur at definite hours in the night, and by the effect of ephedrine and hypnotics in treatment; sleep after an attack possesses a reparative function; if there is no such sleep or it is of short duration the next attack follows more quickly. Attention is drawn to the similarities of the electroencephalogram in sleep and epilepsy. Epilepsy is a periodic illness and is related to the problem of periodicity and rhythm in life processes generally. Sleep and fit show a reciprocal relation to other periodic events—for example, menstruation, which may precipitate fits or have its rhythm disturbed by status epilepticus. *W. Forster*

2243. **Experimental Forms of Human Epilepsy. I. Epilepsy Induced by Intermittent Rhythmical Stimulation by Light.** (Les formes expérimentales de l'épilepsie humaine: 1. L'épilepsie induite par la stimulation lumineuse intermittente rythmée ou épilepsie photogénique)
H. GASTAUT, J. ROGER, and Y. GASTAUT. *Revue Neurologique* [*Rev. neurol.*] **80**, 161–183, March, 1948. 3 figs., 25 refs.

This paper is based on the study of 13 cases of so-called reflex epilepsy or, as the authors prefer to call it, following Penfield and Erikson, " sensory precipitation epilepsy ". The stimulus employed was an intermittent light, and this was found to induce epileptic manifestations, either clinical, electro-encephalographic, or both, in 13 of 317 cases examined. The majority of these were children, some suffering from grand mal, others from petit mal. Manifestations of petit mal were more often induced, and characteristic spike and wave formations in the electroencephalogram accompanied the clinical manifestations, or they might occur alone. The authors propose to continue their investigation using interrupted auditory stimuli. A considerable bibliography is given.
J. St. C. Elkington

2244. **Choreic Encephalitis with Late Development of Parkinsonism. Success of Fever Therapy and of Irradiation of the Corpus Striatum.** (Encéphalite choréique ou chorée prolongée. Evolution tardive vers le parkinsonisme. Succès de la pyrétothérapie par le T.A.B. puis de la radiothérapie des noyaux gris centraux)
G. TARDIEU, B. GUILLAUMONT, and J. SUTTER. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **64**, 334–335, March 5, 12, 19, 1948.

The authors record a case of bilateral chorea of 2 years' duration in a girl of 13, unassociated with any cardiac signs and thought to be of rheumatic origin. The attack subsided rapidly after a course of T.A.B. vaccine injections. One year later the patient returned with a second attack, which responded similarly. A year later a further relapse failed to respond to this treatment but cleared rapidly after a course of *x* rays applied to the basal ganglia. A further relapse a year later responded similarly to radiotherapy. A year later the patient returned with all the features of Parkinsonism, but, after a third course of *x*-ray therapy, made a complete recovery, which has been maintained. The authors are still doubtful whether they were dealing with an unusually prolonged case of Sydenham's chorea or one of encephalitis of choreic type. *J. St. C. Elkington*

2245. **Treatment of Parkinsonism by Irradiation of the Corpus Striatum.** (Traitement des syndromes parkinsoniens par la radiothérapie des noyaux gris centraux)
G. TARDIEU and B. GUILLAUMONT. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* [*Bull. Soc. méd. Hôp. Paris*] **64**, 335–340, March 5, 12, 19, 1948.

The authors report the results of *x*-ray irradiation of the basal ganglia in 14 cases of Parkinson's disease. Striking improvement is recorded in 8 cases, moderate improvement in 3, and none in 2. The duration of the illness did not influence the outcome, but improvement was greater in post-encephalitic cases. At the time of publication no patients treated had been followed up for more than 2 years. *J. St. C. Elkington*

2246. **Aminoaciduria in Progressive Muscular Dystrophy**
S. R. AMES and H. A. RISLEY. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 131–135, May, 1948. 1 fig., 7 refs.

The authors studied amino-acid excretion in 32 patients with progressive muscular dystrophy by determining the amino-acid content of the urine chemically and chromatographically. By both methods it was found that both the number and amount of amino-acids excreted were well above the normal limits as shown by determinations in normal controls. The authors conclude that in progressive muscular dystrophy there is a generalized aminoaciduria. *Ruby O. Stern*

2247. **On the Tensor Fasciae Latae Reflex.** [In English]
E. PEDERSEN. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] **23**, 113–138, 1948. 1 fig., 32 refs.

The author discusses the character and significance of the tensor fasciae latae reflex in health and disease. A brief account is given of the anatomy and embryology of this muscle, and this is followed by a historical survey of the reflex in question. This consists of a sharp contraction of the muscle upon stimulation of the sole of the foot, such as is used in eliciting the plantar reflex. It was found that the reflex was present in 97% of normal subjects of all ages, and was most easily elicited from the inner margin of the sole. In abnormal states it was found to be abolished by interruption of either the afferent or the efferent limbs of the reflex arc, and to be accentuated in conditions where there was damage to the pyramidal tracts. In such cases the reflex was not only more powerful but could be elicited from cutaneous areas outside the normal zone of excitation in the sole.
J. St. C. Elkington

Psychiatry

2248. **Involutional Psychosis: Course when Untreated and when Treated with Electric Shock**
P. E. HUSTON and L. M. LOCHER. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 385–394, March, 1948. 20 refs.

Two series of patients with involution psychoses either of the melancholic or paranoid or mixed type are compared, 1 group having been treated with electric shock and the other not so treated. The paranoid type showed relatively little improvement in both series. Of those who did not receive shock therapy, 52% recovered spontaneously, 20% remained ill, 10% committed suicide, 10% died directly from the disease, and 10% died from other causes; 80% of those treated by shock recovered and the course of their illness was much shortened. Of the 31% who relapsed 80% responded to further series of treatments. The relation between severe symptoms and early suicide or death in the control group is of practical significance in relation to recommendation of early treatment. *R. G. Gordon*

2249. **Encephalographic Investigations of Psychiatric Patients.** [In English]
A. HAUGEN and J. HOVE. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] **23**, 79–93, 1948. 2 figs., 9 refs.

This paper reports the results of air encephalogram examinations in 259 psychiatric patients, including those with psychoneuroses, different varieties of psychosis, pre-senile dementia, and epilepsy. The incidence of various types of ventricular abnormality is recorded, but the relation of these abnormalities to the nature of the psychiatric disorder is not very clear. Reference is made to complications and disturbances following the use of this method. *J. St. C. Elkington*

2250. **Psychiatric Disorders Among the Chronic Sick in Hospital**
J. W. AFFLECK. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 33–45, Jan., 1948. 7 refs.

Between 1907 and 1937, the number of first-attack admissions into the mental hospitals of England and Wales of patients of 65 years and over declined, whereas the corresponding figure in the United States increased. This difference has been explained on the grounds that in England large numbers of such cases were cared for in other institutions or at home, whereas in America less alternative accommodation was provided. It is probable that this trend was reduced in England during the war because of the mobilization of women and the greater difficulty of caring for the patients at home, in nursing homes, and in local hospitals.

The author has undertaken a survey at Leeds of the patients in 5 hospitals governed by the Local Authority Public Health Committee, catering for the chronic sick. Of 788 patients examined (552 women and 236 men), 37·3% had some form of mental disorder; the sexes were nearly equally affected; in the age group 45–65, more than 50% showed mental symptoms. Eighty per cent. of the psychiatric cases had an " obvious organic element in the aetiology of their disorder ", but senile dementia by no means accounted for them all; other forms of organic dementia were frequently found while depressive illnesses, paranoid reactions, mental deficiency, and neuroses all provided a significant contribution. As the result of these findings the author makes various recommendations for the provision of special facilities for the care of the chronic sick with particular reference to the psychiatric aspects of the problem, including the planning of suitable hospitals and the appointment of medical, psychiatric, surgical, orthopaedic, and ophthalmic specialists. The difficulty of attracting adequate numbers of suitable nurses to care for the chronic sick is also discussed in a practical manner.

[This article is based on an examination of existing conditions and should receive careful consideration by those responsible for planning the hospital services.]
P. Mallinson

2251. **Kurt Schneider's Classification of Psychopaths.** (Kurt Schneiders Einteilung der Psychopathien)
A. H. ARNFRED. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] Suppl. 47, 66–74, 1947. 5 refs.

One of the main subjects discussed at the Eighth Congress of Scandinavian Psychiatrists in Copenhagen in 1946 was the problem of psychopathic personalities. Of various suggested classifications the author favours the original classification of Schneider proposed in 1923. An analysis of clinical histories of psychopaths who were treated in mental hospitals in Denmark enabled the author to select and to classify a group of 147 cases. Schneider's classification consists of the following types: the hyperthymic, the depressive, the fanatic, the power-seeking, the emotionally unstable, the explosive, the will-power-lacking, the emotionally rigid, the asthenic and the confidence-lacking types. After giving a short description of these various types the author discusses his group of cases. In mental hospitals the emotionally unstable and the power-seeking psychopath are most commonly met with. The latter group includes the " pathological liar and swindler ". The cases admitted on account of an episodic psychosis, usually precipitated by environmental factors, belonged to the group of depressive and asthenic psychopaths. Comparing his cases with those of Dickmeiss, who as the Chief Police Psychiatrist in Copenhagen also adopted Schneider's classification, the author points out that the anti-social

and delinquent psychopath usually belongs to the " will-power-lacking " or " emotionally unstable " groups. The descriptive classification proposed by Schneider neglects to some extent the deeper psychological analysis, and it must be remembered that the diagnostic label should not prevent the psychiatrist from a more dynamic understanding of each individual case. *J. T. Leyberg*

2252. **Preliminary Studies on a Possible Serum Toxicity in Schizophrenia.** [In English]
T. SJÖVALL. *Acta Psychiatrica et Neurologica* [*Acta psychiat., Kbh.*] Suppl. 47, 105–117, 1947. 16 refs.

It has been suggested that schizophrenia is due to an intoxication of the central nervous system by toxic metabolites produced by some disturbance of the intermediate metabolism. If these toxins are carried to the nervous system by the blood stream it should be possible to detect them, irrespective of their exact chemical composition, by animal experiments. Many workers have claimed to produce evidence that the serum of schizophrenics is more toxic to animals than is the serum of normal human beings. Nevertheless, a critical survey of the literature suggests that so far nothing definite can be claimed. Sera from 24 schizophrenics, hebephrenics, and catatonics and 24 healthy controls were investigated. Each sample was injected into 30 mice. The mice which died did so within 48 hours. The mean number of deaths caused by normal sera was $8{\cdot}2 \pm 2{\cdot}8$; the corresponding figures for sera from schizophrenic patients was $22{\cdot}9 \pm 1{\cdot}8$. It is clear therefore that the latter were more toxic than normal sera. Congo-red, xanthoprotein, and Weltmann tests on the sera, and total albumin determination, gave negative results, thus throwing no light on the nature of the toxin, which, however, seemed to be haemolytic since haemoglobinuria was observed very soon after the injections. This haemolytic principle may be related to the incidence of schizophrenia and especially of acute exacerbations. More work is required, however, to prove for certain that the haemolytic toxin is associated with the schizophrenia and not with secondary factors, such as medication, diet, or special modes of life.
R. G. Gordon

2253. **Pupillary Abnormalities in Schizophrenia and During Muscular Effort**
P. R. A. MAY. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 89–98, Jan., 1948. 6 refs.

Pupillary inequality and reactions to pain, light, and muscular effort were studied in 343 male schizophrenic patients and in 100 male controls all under 55. A constant technique of examination was used. A high incidence of diminished pupillary response to pain, light, and muscular effort was found in a clinically mixed group of schizophrenic patients. Such changes may cause confusion in the differential diagnosis from neurosyphilis. The author believes that both physiological and psychogenic factors are concerned in these phenomena, and that the responses of the pupil can be correlated with the diminished reactivity of the schizophrenic to other stimuli.
E. W. Anderson

2254. **Investigations into the Phenomenon of " Insulin-inhibition " in Schizophrenics.** (Ricerche sul fenomeno dell' " insulino-inibizione " negli schizofrenici)
G. REALE. *Rassegna di Studi Psichiatrici* [*Rass. Studi psichiat.*] **37**, 36–45, Jan.–Feb., 1948. 3 figs., bibliography.

The purpose of this work was to verify the existence of a substance which inhibits the action of insulin in schizophrenia, as postulated by Meduna and others. Blood sugar was estimated in 20 schizophrenic patients, after administration of glucose, at half-hourly intervals for $3\frac{1}{2}$ hours, in the first instance. Glycaemic curves were obtained again a week later after 15 units of insulin had been administered. Individual variations were noted, but they were of no particular significance and were in every way similar to those observed in normal subjects. In view of these results, and taking into consideration other reports on the same subject, the author concludes that there is little evidence at present for admitting the presence of an insulin-inhibitory substance in schizophrenia.
A. Limentani

2255. **Some Observations on the Analytical Group Treatment of a Phobic Patient**
F. KRÄUPL. *Journal of Mental Science* [*J. ment. Sci.*] **94**, 77–88, Jan., 1948. 12 refs.

The author reports in some detail the case of a man of 38 with a travel phobia. The interpretation follows psychoanalytical lines; " anal erotic, sado-masochistic and bi-sexual trends with repressed passive homo-erotic impulses " were noted. Individual treatment before group therapy had proved ineffective. Group therapy diminished the patient's feelings of guilt and induced him to accept certain of these trends. The range of this form of therapy seems to be determined by the group setting as such, as well as by its special composition. Research with groups of different compositions is urged.
E. W. Anderson

2256. **Disturbances of Cortical Function after Electroshock.** (Über nach Elektroschock auftretende kortikale Funktionsstörungen)
A. JUBA. *Schweizer Archiv für Neurologie und Psychiatrie* [*Schweiz. Arch. Neurol. Psychiat.*] **61**, 217–226, 1948. 17 refs.

Observation of patients shortly after electroshock revealed transitory disturbances of cortical functions. As soon as consciousness was regained patients were asked certain questions to test the existence of various forms of agnosia. The author describes in detail 5 typical cases; in all of them the Gerstman syndrome (finger agnosia) was present. Despite the fact that the patients were able to name other parts of the body and the general orientation was good there was inability to recognize and name fingers. The finger agnosia lasted from $\frac{1}{2}$ hour to 2 hours after the shock. When Binet–Simon pictures were shown the description given by the patients referred to separate simple figures, and there was a marked inability to grasp the meaning of the picture as a

whole; the ability to recognize spatial relationship was also disturbed. In 2 of the cases the body-image was slightly distorted. These findings are discussed as indicating a localized disturbance of the left parieto-occipital cortex and special importance is attached to the frequency with which finger agnosia was recorded. This syndrome, according to Gerstman, points to a lesion in the left angular gyrus. The angular cortex (Brodman's area 39) appears to be specially vulnerable to electric stimulation; this may be explained by the fact that it is phylogenetically new and the restitution of its functional integrity takes a longer time. *J. T. Leyberg*

2257. **Electro-encephalographic Patterns in Experimental Epilepsy**
B. L. PACELLA, N. KOPELOFF, and L. M. KOPELOFF. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **107**, 99–104, Feb., 1948. 4 figs., 3 refs.

The application of alumina cream to one side of the brain of monkeys caused the production of chronic recurrent epilepsy with typical electroencephalographic patterns. The principal findings included irregular delta activity, high-voltage spike potential, numerous sharp formations, and fast activity. Bilateral abnormalities with similar activities also occurred. Such changes, observed for periods of from 2 to 5 years, were indicative of the formation of an active epileptogenic zone and in many ways similar to changes noted in constitutional and post-traumatic epilepsy. Subconvulsive doses of "metrazol" increased the focal discharge where the abnormality was limited but did not influence the more abnormal tracings. *A. Limentani*

2258. **Observations on the Effectiveness of Prefrontal Leucotomy in Chronic Schizophrenia.** (Erfahrungen über die Wirksamkeit der präfrontalen Leukotomie bei chronischen Schizophrenien)
H. MICHEL. *Schweizer Archiv für Neurologie und Psychiatrie* [*Schweiz. Arch. Neurol. Psychiat.*] **61**, 256–279, 1948. 9 refs.

After a detailed survey of the literature dealing with prefrontal leucotomy the author describes observations on 12 chronic schizophrenic patients who underwent the operation in the Berne University Clinic. The results were similar to the findings reported by British authors. One patient made a social recovery, 3 improved greatly, 5 improved slightly, and 3 remained unchanged. In most cases there was a definite improvement in affectivity and behaviour; the patients became more sociable, more co-operative, quieter, and much easier to manage. Their behaviour was much less destructive and mischievous. Obsessional symptoms and anxiety were not so noticeable after leucotomy. The operation had no effect, however, upon hallucinations and delusions. Although these may become temporarily less distressing owing to the relief from emotional tension in patients subjected to leucotomy, in the author's view schizophrenic patients with delusions and hallucinations seldom benefit from the operation. The best results were obtained in cases where the pre-psychotic personality was not completely disintegrated. A definite frontal syndrome after the operation was seen in 2 cases only; it is doubtful whether the beneficial effects of leucotomy can be attributed to the formation of a frontal personality change. In view of the fact that all were chronic cases which had failed to respond to other forms of treatment, the results should be regarded as favourable. The duration of the psychosis is of less importance in selecting cases for leucotomy than the symptomatology of the individual case and the degree of preservation of the personality. *J. T. Leyberg*

2259. **Insulin Subshock (Subcoma) Treatment of Psychoses and Psychoneuroses**
D. J. SULLIVAN. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat., Chicago*] **59**, 184–214, Feb., 1948.

The technique described in this paper differs in some ways from the technique of modified insulin treatment commonly used in Britain. The treatment is given twice every day for 4 weeks. The first dose varies from 20 to 30 units of insulin. Each subsequent dose is increased by 5 units until a marked subshock reaction is obtained. The first injection is given at 7 a.m. followed by breakfast at 10 a.m. A second injection is given at 1 p.m. with lunch at 4 p.m. Usual precautions are taken to avoid the occurrence of coma, a sweetened drink being as a rule all that is required to discontinue the subcoma. Adequate subshock reactions are usually obtained in 3 to 4 days. In cases of severe excitement 2 additional doses of insulin are given at 7 p.m. and at 1 a.m. followed by meals 3 hours later. The treatment was carried out in a U.S.A. Military Hospital during 1944 and 1945; in a series of 393 patients there was 1 death from irreversible insulin shock occurring on the fifth day and attributed by the author to a possible allergic response of unknown type. At some time during the 30 days of treatment 10% of the patients had 1 convulsion, this being the only other complication requiring special attention.

In a small group of 69 cases of severe psychoneurosis the response to treatment was immediate. In a second group consisting of psychotic cases there were approximately 300 patients with a diagnosis of "psychosis unclassified, acute schizophrenic reaction". Many of them had been psychotic for 3 or 4 months before reaching hospital from overseas. In most of these patients the condition improved considerably or was in remission at the end of the treatment. Only 10% of patients who were psychotic on admission was eventually transferred to the Veterans' Hospitals. The patients who failed to respond were those with hebephrenic schizophrenia, manic states, and atypical depression. The author therefore believes that insulin in subshock doses is of considerable value in the treatment of the schizophrenic-like psychosis, so frequently met with in military personnel, as well as in the case of undiagnosed psychosis with schizophrenic features. Diagnostic distribution of case material and detailed results are given. A number of cases are reported in full. *A. Limentani*

See also Section Cardiovascular Disorders, Abstract 2129.

Infectious Diseases

VIRUS INFECTIONS

2260. **Experimental Attempts to Transmit Phlebotomus (Sandfly, Pappataci) and Dengue Fevers to Chimpanzees**
J. R. PAUL, J. L. MELNICK, and A. B. SABIN. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **68**, 193–198, May, 1948. 3 figs., 10 refs.

Six chimpanzees were inoculated subcutaneously (0·5 to 0·9 ml.) and intracutaneously (0·5 to 0·9 ml.) with human serum collected from natural cases of phlebotomus fever and stored on dry ice for about 3 years. (Sabin has found human serum to be infective after 4 years of storage on dry ice.) None of the animals exhibited any sign of illness other than fever, which was measured in only 2 of them, and the very slight temperature rise which occurred in these 2 animals cannot be interpreted with certainty. In the absence of leucocyte studies and subinoculation tests in human volunteers, there is no evidence to indicate one way or another whether chimpanzees are susceptible to this virus. Nine chimpanzees, including 4 of those used in the above experiment, were inoculated subcutaneously with human dengue virus from Hawaii. There was no clinical evidence of infection or striking elevation of temperature. However, those whose serum was tested were shown to have developed neutralizing antibodies to the homologous mouse-adapted dengue virus following inoculation.

F. O. MacCallum

2261. **Observations on Post-measles Encephalitis.** (Contributo allo studio delle encefaliti postmorbillose)
G. BROGI and L. LANDUCCI. *Rivista di Clinica Pediatrica* [*Rev. Clin. pediat.*] **46**, 83–97, Feb., 1948. 6 figs., 28 refs.

From the Paediatric Department of the University of Siena the authors report 4 cases of post-measles encephalitis, in children aged 5, 7, 4½, and 9 years respectively. These cases were observed during an epidemic of measles in Tuscany between March and August, 1946. In all cases the neurological complication began after the disappearance of the rash and the onset was either sudden or slowly progressive, with or without pyrexia. In the first case there was an ataxic syndrome, in the second catatonia and aphasia, and in the third convulsions and, on discharge, a moderate ataxia. These 3 children recovered completely. The second child, who was critically ill, improved dramatically after administration of serum from a patient who had just recovered from post-measles encephalitis. The fourth child was admitted in convulsions and coma and was discharged 12 hours after admission at the parents' request.

The authors discuss 3 theories of the aetiology of post-measles encephalitis: invasion of the nervous system by the virus of measles, activation of a latent virus, and an allergic reaction taking place in the nervous system. The authors on the whole are in favour of the theory of activation of a latent virus, a view which is supported by the result of treatment in their second case. This patient responded to serum from a post-encephalitic case, while another did not respond to administration of parental serum.

[Barnes *et al.* (*Lancet*, 1937, **1**, 687) reported a favourable result from the use of serum obtained from a patient who had recovered from post-measles encephalitis.]

P. E. Polani

2262. **Evaluation of Aids to Muscle Reeducation in the Treatment of Poliomyelitis**
F. J. KOTTKE, B. S. TEIGEN, S. SIEGEL, and M. E. KNAPP. *Archives of Physical Medicine* [*Arch. phys. Med.*] **29**, 141–147, March, 1948. 5 figs., 7 refs.

The diminution of muscle spasm in poliomyelitis by the use of hot packs, neostigmine, and curare has been advocated. An attempt was made by the authors in the Minnesota epidemic of 1946 to evaluate objectively the use of hot foments and curare as adjuvants to the standard physical measure of gentle passive stretching for muscle spasm and shortening in the subacute stage of the disease. The results are summarized in 17 cases treated within 2 weeks of the onset of the disease. In 5 patients only stretching, or injection of saline and procaine with stretching, was carried out. Four received hot foments and stretching, and 8 received curare (about 1·5 units per kg. of aqueous " intocostrin ") and stretching. Curare was not found to relieve the pain caused by stretching muscles in spasm. In 1 case spasm developed in a new muscle group in a patient who was already receiving curare. None of the adjuvant measures used had any significant effect on the spasm and shortening. The authors suggest that careful stretching alone is all that may be necessary.

Andrew Zinovieff

2263. **On the Preparation of a Formalinized Aluminium hydroxide Vaccine with the Murine S.K. Poliomyelitis Strain (Jungeblut and Sanders).** [In English]
A. FRANTZEN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 351–355, 1948. 5 refs.

The mouse-adapted SK strain of poliomyelitis virus was grown in tissue culture consisting of embryo mouse brain in Tyrode solution in an atmosphere containing from 2 to 6% of carbon dioxide. Passages were made every 48 hours and incubation was carried out at 35° C. After 23 passages the titre of the supernatant fluid was 10^6. It was removed and neutralized with hydrochloric acid to *p*H 7·4, and a slight precipitate which formed was removed by centrifugation. Aluminium hydroxide gel was then added in the proportion of 1 part of gel to 4 parts

of culture supernatant. The gel was then removed by centrifugation and resuspended in buffered saline of *p*H 7·38. Titrations showed that the gel had adsorbed most of the virus, since the titre of the supernatant fluid had fallen from 10^6 to 10. The virus was inactivated by treating the gel suspension with 0·1% formalin at 25° C. The inactivated suspension was then used in immunization experiments which are described in the following paper. [See Abstract 2264.] *D. J. Bauer*

2264. **Mice Immunization Tests with Various Poliomyelitis Vaccines and Sera.** [In English]
F. KAUFFMANN and A. FRANTZEN. *Acta Pathologica et Microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **25**, 356–359, 1948. 3 refs.

A vaccine was prepared with the SK strain of murine poliomyelitis virus by adsorption on to aluminium hydroxide according to the method described in Abstract 2263. From 1 to 6 doses of the vaccine were given to mice by intraperitoneal injection at intervals of 3 to 4 days; at the end of the course of vaccination living SK virus was given intraperitoneally in varying doses. In this way it was found that 4 doses of vaccine conferred protection against a challenge dose of 1,000 LD 50, while 2 doses conferred a definite but lesser degree of immunity. A vaccine prepared by treating mouse brain containing SK virus with formalin was also tested, and was found to be as effective as the aluminium-hydroxide type of vaccine. Vaccine was also prepared with Theiler's FA strain of murine poliomyelitis virus. This protected against subsequent infection with FA virus, but not with SK, and conversely SK vaccine did not protect against subsequent infection with FA virus, showing a lack of serological relationship between these 2 strains. Similar results were also obtained in cross-neutralization tests. In conclusion, the work is considered in the light of its possible bearing upon active immunization against poliomyelitis in human beings; it is pointed out that the murine strains would probably be too remote in their antigenic composition to be of any value in human immunization. *D. J. Bauer*

2265. **The Neutralization of the Mouse-adapted Poliomyelitis Virus by the Sera of Patients, Family Contacts, and Normal Children in Los Angeles**
C. F. PAIT, J. F. KESSEL, and P. GROSSMAN. *American Journal of Hygiene* [*Amer. J. Hyg.*] **47**, 335–344, May, 1948. 2 figs., 8 refs.

With the adaptation of certain strains of poliomyelitis virus to small laboratory animals, investigation of serological problems became easier. A number of such studies have now been reported, the Lansing strain of virus usually being employed as antigen. It had been hoped that with this strain and paired human sera from cases of poliomyelitis, it might be possible to demonstrate a rise in antibody. The hope that such a test could be useful in diagnosis has not been fulfilled, mainly because antibody is so often found in the acute phase sample of serum from cases of the disease, and the present study contains further confirmation of this point.

Additional observations of interest were as follows Neutralizing antibody was found in a high proportion of human sera from persons with no history of clinical poliomyelitis. Tests on the serum of 9 young mothers before labour and on the serum of their offspring at the time of delivery showed complete correspondence; when antibody was present in the mother's serum it appeared in the baby's serum in equal quantity. Tests on the sera of children in different age groups showed that from 0 to 5 months, 16 of 22 were positive (72·7%), whereas from 6 to 11 months only 4 of 15 were positive (26·6%), and from 12 to 23 months likewise only 4 of 15 were positive. After the age of 2 the percentage of samples neutralizing Lansing virus steadily increased from 63·6 at 2 to 3 years to 83·3 at 8 to 11 years, which latter figure corresponds to the findings in adults.

[The interpretation of the significance of antibody tests with Lansing virus is still uncertain, partly because the antigenic relation of this strain to monkey-pathogenic strains is imperfectly understood.] *A. J. Rhodes*

2266. **The Relationship Between the Antipoliomyelitic Properties of Human Nasopharyngeal Secretions and Blood Serums**
E. J. BELL. *American Journal of Hygiene* [*Amer. J. Hyg.*] **47**, 351–369, May, 1948. 3 figs., 37 refs.

It has been known for many years that nasal washings may neutralize poliomyelitis virus, but this property has been held to be non-specific. The author now reports studies suggesting that the neutralizing substance is antibody.

Nasopharyngeal secretions were collected by a special technique. Neutralizing tests were carried out in mice, the Lansing strain being used as antigen. The secretions of 32 to 68 " normal " adults (in Baltimore) neutralized the Lansing strain of poliomyelitis virus. The serum of 51 of 68 persons also neutralized and that of 17 persons failed in this test. Of 32 persons with secretions that neutralized the virus all but 2 showed serum antibody as well. Of the 51 whose serum neutralized, fewer than two-thirds had positive secretions. It appeared that antibody " spilled over " from the serum above a certain level. In further support of the claim that the neutralizing substance in the secretions is specific antibody, it was found that the St. Louis encephalitis and Western equine encephalomyelitis viruses were not neutralized.

It is interesting to speculate whether the presence of antibody in the upper respiratory tract plays any part in hindering invasion of virus in this area. *A. J. Rhodes*

2267. **The Changes in the Serum Proteins in Patients with Experimentally Induced Infectious Hepatitis**
W. P. HAVENS and T. L. WILLIAMS. *Journal of Clinical Investigation* [*J. clin. Invest.*] **27**, 340–345, May, 1948. 4 figs., 21 refs.

During an extensive study of acute infective hepatitis experimentally produced in healthy male human volunteers alterations in the serum proteins were examined by a method of differential precipitation. All the 29 patients

were jaundiced. It was found that the alterations follow a regular pattern. Nothing much happens until the period of defervescence at the end of the first week, when there is a striking decrease in serum albumin and increase in serum globulin so that the normal albumin–globulin ratio is completely reversed. The main increase is in euglobulin, but pseudoglobulin also rises. Serum albumin returns to normal in 5 weeks, but serum globulin remains above normal for as long as 3½ months.

J. W. McNee

2268. **Results of Heterophile Antibody Agglutination and Kahn Tests in Patients with Viral Hepatitis**

W. P. HAVENS, J. M. GAMBESCIA, and M. KNOWLTON. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol., N.Y.*] **67**, 437–440, April, 1948. 11 refs.

Heterophile antibody agglutination, Kahn, and cold agglutinin tests were carried out in two groups of patients suffering from virus hepatitis. The first group comprised 30 healthy volunteers, in whom all tests had previously been negative. The second group were patients from an army hospital who were known not to have syphilis. The first group failed to develop heterophile antibodies, while sera from 3·3% of the second group showed titres of 1 : 56, the majority after 2 to 5 weeks, which were reduced to 1 : 7 or became negative after absorption on boiled guinea-pig kidney. In one of the volunteers, who suffered from a *Salmonella cholera suis* bacteriaemia, there was a positive Kahn reaction in the second week, which reverted to negative in the seventh week. Of the second group 1·7% gave a positive Kahn reaction, mainly during the first 2 weeks, which became negative after varying periods. None of the volunteers developed cold agglutinins, while 0·6% of the second group did so to a titre of 1 : 32, the reaction becoming negative after 1 week.

R. Salm

BACTERIAL INFECTIONS

2269. **Bone and Joint Lesions in Leprosy: A Radiologic Study**

G. ESGUERRA-GÓMEZ and E. ACOSTA. *Radiology* [*Radiology*] **50**, 619–631, May, 1948. 24 figs., 10 refs.

The authors analysed the radiographic and clinical findings in 483 lepers. In 306 of these there were varying degrees of mutilation of the digits. Radiographically the phalanges might show a degree of decalcification sometimes associated with a form of osteitis multiplex cystica. In the terminal phalanges there were varying degrees of absorption. Joint destruction with softening and pressure deformities, and neurotrophic joints with destruction of the joint surfaces, were observed. In 177 of the cases skin lesions prevailed with little or no clinical sign of skeletal destruction, but on radiographic examination about half of these patients were found to have decalcification of the phalanges, and in 68% there were bone changes suggestive of leprosy.

James F. Brailsford

2270. **Action of Streptomycin on Leprosy.** (Über die Wirkung des Streptomycins auf Lepra)

J. GRILLO. *Zeitschrift für Hygiene und Infektionskrankheiten* [*Z. Hyg. InfektKr.*] **127**, 588–591, April, 1948. 2 figs., 7 refs.

It has been observed that substances such as certain sulphones are beneficial in tuberculosis and also in leprosy; the author therefore tried streptomycin (which is of proven value in certain types of tuberculosis) in a case of leprosy. The treatment caused a pronounced clinical improvement as well as a reduction in the acid-fast bacilli in the skin, lymph nodes, and lepromatous nodules. The case was a fairly severe one and treatment with streptomycin was given for 3 months. At first, 4 g. was injected daily, 0·5 g. being given intramuscularly every 3 hours, and after only 12 days there was a noticeable improvement and a diminution in the leproma. After a total dose of 300 g. had been given the daily dose was reduced to 2 to 3 g. every 4 or 6 hours. The total amount eventually administered was 360 g. Certain slight toxic reactions were observed, but it was not necessary to cease the treatment.

R. Wien

2271. **Calciferol Treatment of Leprosy. Preliminary Report of Two Cases**

H. T. CHAGLASSIAN. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **10**, 303–304, May, 1948. 3 refs.

Two cases of tuberculoid leprosy were treated by the administration of calciferol. There was such pronounced improvement in both cases that the author is planning further experiments in a larger group of patients.

G. B. Mitchell-Heggs

2272. **Penicillin and Sulphathiazole in Typhoid Fever**

G. BEVAN, R. EVANS, I. PUGH, M. V. N. SUDDS, M. T. PARKER, and A. F. S. SLADDEN. *Lancet* [*Lancet*] **1**, 545–550, April 10, 1948. 7 refs.

The typhoid fever outbreak in Aberystwyth in July–August, 1946, was attributed to infection of ice-cream by a urinary carrier; there were 202 cases, a high proportion of which were in children. The infecting organism was shown to be a strain of Vi-phage type C. The cases as a whole were not of a very severe type, the case fatality rate for the outbreak being 3·6%, compared with 9·6% in the milk-borne outbreak of 1936 in Bournemouth and 14% in the water-borne outbreak of 1937 in Croydon. While the low mortality rate may be partly explained by the relative mildness of the disease in the children, something appears to have been accomplished by administration of penicillin, sulphathiazole, and Felix's anti-typhoid serum. Of the 25 patients treated with this combination none died, and these included 5 whose condition caused the gravest anxiety. However, in the 39 cases treated by penicillin–sulphathiazole in the dosage suggested by McSweeney the speedy disappearance of toxaemia and subsidence of pyrexia described by McSweeney were not observed. This is an important finding because the number of cases treated was considerable, and included 26 controlled cases in which the treatment had no appreciable clinical effect. Further,

a considerable proportion of patients yielded positive blood cultures shortly after completion of the penicillin–sulphathiazole treatment, and faecal excretion of typhoid bacilli during convalescence was not shorter in the treated groups than in the controls.

The treatment was given in 3 different hospitals. Very few children were included in the investigation, in view of the tendency to mildness of the disease in children. The dosage of penicillin and sulphathiazole followed very closely that suggested by McSweeney, namely, two courses of 10,000,000 units of penicillin and 34 g. of sulphathiazole, each course lasting for 4 days. The authors state clearly that this dosage was ineffective in the treatment of the severe type of case; they had, however, no opportunity of testing the effect of doubling the dose of penicillin or increasing it even further. Tests for sensitivity of the type C strain isolated in the outbreak showed it to be slightly more sensitive than 4 strains of other phage types. [The results of these tests are not given in quantitative terms and will be reported elsewhere.] The authors are so convinced of the negative results of this investigation that they consider it necessary to warn against the indiscriminate use of penicillin–sulphathiazole in the treatment of typhoid fever.

H. Stanley Banks

2273. **Comparative Efficiency of Rectal Swabs and Fecal Specimens in Detecting Typhoid and Salmonella Cases and Carriers**

H. J. Shaughnessy, F. Friewer, and A. Snyder. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **38**, 670–675, May, 1948. 8 refs.

The superiority of examination of rectal swabs over stool examination in the diagnosis of bacillary dysentery being well known, the authors decided to compare the efficiency of these two methods in the diagnosis of typhoid and salmonella infections. Forty-three patients with histories of a typhoid or salmonella carrier state were investigated, the cases being selected so that persistent, intermittent, and infrequent carriers were all represented. Pre-cathartic rectal swabs and stools were collected from each patient on the same day. On this day the patients were given bile salts and, on the following day, a saline cathartic. Two rectal swabs and a stool specimen were collected from each patient after the first bowel movement. An attempt was also made to collect 6 series of pre-cathartic and post-cathartic specimens from each patient, but was not always successful. As soon as collected, one swab was plated on Hajna–Perry agar and the other inoculated into a tube containing 2 to 3 ml. of selenite medium. On the following morning the growth from the latter was streaked on to S.S. medium. The specimens of stools were similarly dealt with.

The results showed that when specimens containing many bacteria were examined neither of the methods was markedly superior, but when the specimens contained apparently few organisms examination of the stool was more reliable than that of the swab. The post-cathartic specimens gave a greater percentage of positive results than the pre-cathartic. It was found that no single medium could pick up all intestinal pathogens.

Opportunity for a further experiment arose when a case of typhoid fever occurred in a mental hospital. The 189 patients in the ward were divided into two approximately equal groups. In one group rectal swabs were taken, while in the other post-cathartic specimens were collected. Three days later, swabs were taken from the second group and post-cathartic specimens from the first group. *Salmonella typhi* was isolated from 7 patients. Only 3 of these positive results had been obtained from swabs, while in all 7 cases the post-cathartic specimens were positive. Subsequently, beginning about 12 days after the original specimens were collected, 2 sets of pre-cathartic and post-cathartic specimens were collected in each of the 7 cases. All of the post-cathartic specimens except 1 were positive, while 4 of the pre-cathartic specimens were negative.

R. B. Lucas

2274. **Influence of Sensitization on the Development of Antitoxin Immunity and on the Course of Diphtheritic Infection in Immunized Subjects.** (Влияние сенсибилизации на развитие антитоксического иммунитета и на течение дифтерийной инфекции у вакцинированных животных)

S. Y. Feigina. Педиатрия [*Pediatriya*] No. 2, 15–22, March–April, 1948.

The experimental work described is based on the assumption that in clinically severe diphtheria, apart from a low level of immunity in the individual, allergic manifestations may play an important part. It is further assumed that these allergic symptoms are not only produced by specific diphtheria antigens with which a patient may have been in contact previously but that they may be ascribed also to non-specific bacterial or other proteins.

In the first series of experiments one group of 11 guinea-pigs received 2 mg. of B.C.G. vaccine subcutaneously and 9 rabbits 5 to 10 mg. intravenously. A second group of 10 guinea-pigs was given 1 ml. of typhoid-paratyphoid vaccine, and a third group of 10 guinea-pigs 1 ml. of a killed broth culture of streptococci. A control group of 7 guinea-pigs was immunized with 1 dose of toxoid and later given an injection of a diphtheria bacillus culture. In all 3 groups, the "sensitizing factors" were administered together with diphtheria anatoxin (toxoid) of Lf 30. After 36 days the state of sensitization of the first group was checked by the Mantoux test and the state of immunity by Schick testing with a 5-fold dose. All animals were Mantoux-positive; 8 guinea-pigs were Schick-negative and in 3 the reaction is described as a necrosis, exceeding greatly in 2 the reaction in non-immunized control animals. A day later the guinea-pigs were inoculated intratesticularly with 1 MLD of the gravis strain 155 of the diphtheria bacillus, this dose corresponding to 200 million organisms in 0·1 ml.

The 8 Schick-negative guinea-pigs developed a local hyperaemia and oedema within 24 hours which disappeared within 3 to 5 days. Of the 3 Schick-positive guinea-pigs the 1 with the less severe necrosis died with the usual signs of diphtheria while the other 2, although

they had severe local reactions, had no general symptoms and their death on the third and fourth days respectively came as a surprise. At post mortem the changes were restricted mainly to the scrotum—necrotic inflammation and gross oedema—while the testes appeared almost normal; there was only slight hyperaemia of the adrenals, and in 1 animal a small area of consolidation in the right lower lobe of the lung. These findings were regarded as insufficient to explain death from diphtheria. Histologically these animals, in contrast to the control animals, had a marked myocardial dystrophy. Three of the 9 rabbits treated likewise showed no immunity to diphtheria, and when injected with the *Corynebacterium diphtheriae* culture in the same way 2 of these animals died. At post-mortem examination local signs of inflammation were very severe. Histologically, myocardial dystrophy was again marked. All 10 guinea-pigs inoculated with combined A.P.T. and T.A.B. were immune and survived infection. In the third group immunity seemed to have been lowered by the administration of streptococcal vaccine together with diphtheria toxoid; only 2 guinea-pigs were Schick-negative while 5 of the 7 control animals were Schick-negative.

These experiments were repeated, 2 and 3 injections of diphtheria toxoid being given after preliminary " sensitization "; while all animals survived infection, it was observed that: (1) the local reaction was greater than would have been expected without " sensitization "; (2) guinea-pigs " sensitized " with streptococcal vaccine had a considerably lower antitoxin level than those in the other 2 groups. The changes at the site of infection and in the myocardium are regarded as allergic manifestations to the infecting organism and it is suggested that similar reactions in man may account for the clinical severity of diphtheria infections.

[The paper suffers from insufficient numbers of experimental animals, lack of conciseness, and the complete absence of references.] *K. S. Zinnemann*

2275. **Restoration of Diphtheria Immunity without Injections (Bousfield's Method)**
P. MASUCCI, H. GOLD, and R. J. DEFALCO. *Journal of Pediatrics* [*J. Pediat.*] **32**, 35–38, Jan., 1948. 6 refs.

This investigation in a series of 37 subjects confirms Bousfield's findings that diphtheria toxoid can pass across the mucous membranes of the upper alimentary tract. The amount absorbed was only sufficient to act as a " booster " dose and primary immunization by this method does not appear feasible. The toxoid, 100 Lf units, was incorporated in a compressed tablet and three tablets were given daily for 7 days. The tablets were kept under the tongue and sucked slowly. No inconveniences or reactions were observed. The large total dosage required may restrict the practical application of this method to adults, in whom severe constitutional disturbances after a parenteral injection of diphtheria toxoid are not uncommon. *H. Herlinger*

See also Section Hygiene and Public Health, Abstracts 1942–4.

2276. **The Treatment of Pertussis and Pneumonia Complicating Pertussis. The Role of Hyperimmune Gamma Globulin and Sulfadiazine**
H. BRAINERD. *Journal of Pediatrics* [*J. Pediat.*] **32**, 30–34, Jan., 1948. 18 refs.

The author treated 26 infants suffering from pertussis with hyperimmune gamma globulin (agglutinating titre of at least 1 in 15,000), injecting 2·5 ml. intramuscularly on each of 4 successive days. In addition sulphadiazine, in doses of 130 mg. per kilo a day, was given to another 26 infants in whom pertussis was complicated by pneumonia. The mortality in this latter group was only 7·7%. The response to treatment was often dramatic, so far as general appearance and defervescence were concerned, though cough and whoop disappeared more slowly. In the uncomplicated group symptomatic results—that is, diminution of cough, whoop, and vomiting—were " more notable " than in the other series; but again the effect of the treatment in reducing mortality and preventing complications was " superior to the relief of symptoms ". The best results were obtained if treatment began in the first 7 days of illness. *H. Herlinger*

2277. **Streptomycin in the Treatment of Complicated Whooping Cough.** (La streptomycine dans le traitement des coqueluches compliquées)
J. CATHALA, R. BASTIN, LE TAN VINH, —. STRAUS, and F. CHAVELET. *Semaine des Hôpitaux de Paris* [*Sem. Hôp. Paris*] **24**, 1329–1330, May 30, 1948.

The authors report an investigation into the value of streptomycin in the treatment of pertussis of the worst grades of severity. They record treatment of 3 infants, from 2 to 7 months old, with spasms due to asphyxia. Two died within 24 hours of admission to hospital after receiving not more than 3 injections of streptomycin, but the third, an infant of 2 months, recovered after receiving 0·05 g. (50,000 units) daily for 11 days. The authors state their certainty that the life of this baby was saved by streptomycin. Of 7 older children with serious pulmonary complications 6 recovered after receiving for 8 days a dose of 300,000 units (0·3 g.) daily. It is concluded that the value of streptomycin in pertussis cannot be doubted, and that the toxic-infective element in the disease is more amenable to treatment than what the authors call the neuro-vegetative element. By this they mean that though the patient's life may be saved and the general severity of all symptoms much abated streptomycin will not completely abolish the spasms of coughing which may persist for long periods. In the asphyxial spasms of infants the effect is stated to be indubitable, the course of the disease being cut short provided that the patients are able to survive the first 2 or 3 days. Finally, a case of " whooping-cough encephalitis " is described in a child of 10 who recovered after 5 days' treatment with 400,000 units daily, with complete disappearance of numerous paralyses. [One may perhaps doubt the diagnosis in this case. A true encephalitis has not been convincingly demonstrated in pertussis. It is not improbable that the various symptoms detailed were due to temporary cerebral anoxaemia.] *Jos. B. Ellison*

2278. **Cerebral Complications in Pertussis**
A. M. LITVAK, H. GIBEL, S. E. ROSENTHAL, and P. ROSENBLATT. *Journal of Pediatrics* [*J. Pediat.*] **32**, 357–379, April, 1948. 9 figs., 49 refs.

This paper presents an analysis of 47 cases of clinical cerebral complications occurring in 6,002 patients admitted to hospital over a period of 15 years, an incidence of 0·8%. Whilst the mortality rate from pertussis has dropped significantly since the introduction of sulphonamide therapy, there has been no corresponding drop in the mortality rate in patients with cerebral complications. In the majority of the authors' cases (72·5%) cerebral complications developed during the third and fourth weeks of the disease. The onset was almost always accompanied by a rise in temperature and a convulsion and 50% of the patients were under 12 months of age. The cerebrospinal fluid was examined in 38 of these cases. In all cases the fluid was clear and sterile on culture and in only 7 was the cell count in excess of 15 per ml. The various theories that have been advanced about the aetiology of cerebral complications are discussed in some detail. Nineteen of these 47 children died. In general terms it may be stated that one-third of patients with cerebral complications die in the acute phase; one-third recover but develop sequelae; and one-third recover completely. A follow-up of a small number of these patients led the authors to conclude that, if pertussis is complicated by cerebral manifestations, the nervous system becomes vulnerable to further injury. A study was made of the pathology of the brains of 34 infants and children who died of pertussis. No inflammatory reactions were observed, and the changes present were considered to be due to vascular or degenerative damage consequent upon anoxia and not inflammation. For these reasons the term encephalopathy is preferred to encephalitis. Treatment is essentially symptomatic. Six typical case reports are presented.

Jas. M. Smellie

2279. **Pulmonary Brucellosis**
W. A. HARVEY. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 768–781, April, 1948. 5 figs., bibliography.

Brucellosis (abortus) is increasing, or being more widely recognized, in various regions of the world and is hyperendemic in some areas of the United States, but, owing to the equivocal laboratory and diagnostic criteria, the author believes that diagnosis tends to be made on insufficient grounds and that the condition is missed because the clinical picture may be so atypical as to escape recognition. In support of this contention the author cites two cases of pulmonary brucellosis in adult women. The first case was diagnosed retrospectively as the result of routine radiography which revealed (symptomless) interstitial pulmonary fibrosis. Enquiry elicited a previous history of a long febrile illness associated with cough, abundant sputum, cervical, axillary, and hilar adenopathy, and splenomegaly. When the patient came under the author's care, save for the radiographic signs, persistent enlargement of external groups of lymph nodes, and splenomegaly, there was little amiss clinically, but *Brucella abortus* was agglutinated to a titre of 1 in 80, and the opsonocytophagic test was positive (25 cells), although blood cultures and reactions to skin tests were negative. Tentative retrospective diagnoses of other conditions were excluded after consideration of the appropriate laboratory findings.

In the second case, with a similar clinical history, chronic tuberculosis with infiltration of both lungs was diagnosed and the patient was ultimately admitted to a sanatorium where, except for the radiographic signs, no evidence of tuberculosis could be discovered and the patient was discharged. Further laboratory tests included those for brucellosis and these revealed agglutination of *Br. melitensis* to 1 in 320 and *Br. abortus* to 1 in 1,280 (strong) and 1 in 5,120 (slight). The Lederle–Fegrile antigen reaction, the opsonocytophagic reaction, and the brucellergen reaction were strongly positive. The author considers that in the absence of a positive blood culture (rare in chronic brucellosis), diagnosis is not established unless two of the specific reactions are positive. Of these, in spite of its admitted imperfections, agglutination, considered in the light of the clinical history and findings, is the most reliable. [See, however, Abstract 2280.] *E. H. R. Harries*

2280. **Brucella Antibodies Following Cholera Vaccination**
C. W. EISELE, N. B. MCCULLOUGH, and G. A. BEAL. *Annals of Internal Medicine* [*Ann. intern. Med.*] **28**, 833–837, April, 1948. 8 refs.

Brucella agglutinins may appear in significant titres after vaccination against cholera and may thus cause confusion in the diagnosis of brucellosis among the previously inoculated. Of 20 volunteers who before inoculation with the standard 2 doses of cholera vaccine gave a negative response to brucella agglutination and opsonocytophagic tests and, with one exception, to brucellergen, all developed brucella agglutinins. Agglutination tests were made at intervals of 2 to 3 weeks, 8 weeks, 18 weeks, and 1 year after cholera inoculation. In 4 the titres did not exceed 1 in 20, but in the remaining 16 titres ranging from 1 in 40 to 1 in 320, and in 1 exceptional case 1 in 2,560, were recorded at the first test. Titres were maximal at the first or second tests and thereafter declined. The opsonocytophagic reaction was positive in a degree parallel with the agglutination titres in 16 of the 20 volunteers. Both reactions were positive in a proportion of trials after an interval of a year. It is important to observe that, except in the one case already mentioned, brucellergen reactions remained consistently negative. Of 100 men who had been inoculated against cholera 56% had brucella agglutinins in titres of 1 in 20 or higher. In 41% the titres were 1 in 40 or higher (in 20% 1 in 80 or 1 in 160). It is reasonable to suppose that anamnestic responses may occur long after the original brucella agglutinins have disappeared and thus add still further to the difficulties of diagnosis of brucellosis, particularly chronic brucellosis. The authors, while agreeing that the agglutination test is the most widely used for diagnosis, deplore the fact that titres of 1 in 80 or 1 in 160 are commonly accepted as diagnostic in the

presence of a great variety of symptoms. In Iowa brucellosis is an occupational disease for which compensation may be obtained, and a brucella agglutination titre of 1 in 160 at two successive tests is held to verify a clinical diagnosis. The authors point out that most of the subjects of the present investigation would qualify for compensation. In previous studies on *Vibrio comma* and brucella the authors found that the cross-antibody response is due to an H-antigen of *V. comma* and they suggest that absorption tests with cultures of *V. comma* and of brucella, together with the fact that cholera vaccine does not cause a positive brucellergen reaction [in itself unreliable], might provide diagnostic assistance in doubtful cases which may arise among the millions of men who were inoculated against cholera when on service.

E. H. R. Harries

See also Section Hygiene and Public Health, Abstract 1951.

2281. **Prophylactic Immunization and Specific Therapy of Experimental Pneumonic Plague**

K. F. MEYER, S. F. QUAN, and A. LARSON. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **57**, 312–321, April, 1948. 6 figs., 7 refs.

Intranasal instillation under anaesthetic of 2,000 to 25,000 highly virulent plague bacilli produces in mice, guinea-pigs, and cotton rats a confluent bronchopneumonia anatomically indistinguishable from that observed in pneumonic plague in man. Guinea-pigs are more resistant than mice.

Active immunization of guinea-pigs and mice with avirulent strains of *Pasteurella pestis* or chemically-killed plague bacilli precipitated with alum conferred on them a definite degree of protection against intranasal infection with virulent bacilli (60% of mice were protected against flea-bite infection; only 25% against intranasal infection; 80% of guinea-pigs resisted intranasal infection). Concentrated antiplague rabbit sera have some prophylactic and a very slight curative effect in pneumonic plague. Sulphonamides, which have little effect alone in pneumonic plague, are much more effective when combined with antiplague serum. Over 90% of experimentally infected mice may be cured with 5 mg. of streptomycin, even in the septicaemic stage. It is therefore recommended that pneumonic plague in man should be treated with 4 to 6 g. of streptomycin daily for 6 to 10 days at least.

C. L. Oakley

TUBERCULOSIS

2282. **The Action of *p*-Aminosalicylic Acid (PAS) in Experimental Tuberculosis**

W. T. MCCLOSKY, M. I. SMITH, and J. E. G. FRIAS. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **92**, 447–453, April, 1948. 2 figs., 10 refs.

After investigating the acute and chronic toxicity of *p*-aminosalicylic acid (PAS) and its rate of absorption and excretion in laboratory animals, its chemotherapeutic activity in tuberculosis, both alone and in combination with streptomycin therapy, was studied in guinea-pigs and rabbits. In guinea-pigs the infective dose of tubercle bacilli was 0·5 mg. moist weight of human strain A27 intraperitoneally; treatment was started the next day and continued for 11 weeks; survivors were killed at 14 weeks. The three treatment groups received, respectively, PAS orally once daily 0·5 g. per kilo of body weight; streptomycin 10 mg. per kilo body weight twice daily parenterally; PAS and streptomycin. A fourth group served as controls.

The effectiveness of the treatment was based on survival times and on the degree of visceral involvement, as compared with the controls. On these criteria the effectiveness of PAS was very slight; that of streptomycin was very considerable; and that of combined treatment was so little more than that of streptomycin alone as to indicate merely an additive, rather than a potentiating, effect—thus showing a difference from the combination of sulphones with streptomycin. Similar results were obtained with rabbits and a bovine strain of tubercle bacilli.

[The relative ineffectiveness of PAS in experimental tuberculosis conflicts with the more favourable findings of other workers (see *Abstracts of World Medicine*, 1948, **3**, 666, and Abstract 2283); in an addendum the present authors discuss the first of these papers (Feldman, Karlson, and Hinshaw) and seek to account for the differences in terms of experimental conditions.]

P. D'Arcy Hart

2283. **Experimental Study of Antituberculous Action of *para*-Aminosalicylic Acid.** (Étude expérimentale des effets antituberculeux de l'acide 4-aminosalycylique)

C. LEVADITI, A. GIRARD, and A. VAISMAN. *Bulletin de l'Académie Nationale de Médecine* [*Bull. Acad. nat. Méd., Paris*] **132**, 210–214, March 16 and 23, 1948. 9 refs.

The protective effect of PAS in mice experimentally infected with tuberculosis was definite though inferior to that of streptomycin. The effect of the latter was not improved by simultaneous administration of the two drugs. [See *Abstracts of World Medicine*, 1948, **3**, 666, and Abstract 2282.]

P. D'Arcy Hart

2284. **Treatment of Non-cutaneous Tuberculosis by Vitamin D_2.** (Traitement de différentes formes de tuberculose non cutanée par la vitamine D_2)

R. DESMEULES, L. ROUSSEAU, P. RICHARD, and C. H. DORVAL. *Laval Médical* [*Laval méd.*] **13**, 273–285, March, 1948. 19 refs.

In 1943 lupus was first treated by calciferol injections, and these were given in 1946 for tuberculous empyema after artificial pneumothorax. For these cases, a solution of vitamin D_2 containing 300,000 i.u. per ml. was used. Three doses of 600,000 i.u. were given in the first week, followed by 5 doses of 200,000 i.u. 3 times a week for a period varying from 1 month to 8 months, according to individual tolerance. There was a slight risk of arterial calcification after such high doses taken over a long period. Various laboratory tests were made

before and after treatment, the chief of these being estimations of calcium and phosphatase levels in blood.

The results in 55 cases of non-cutaneous tuberculosis treated were most remarkable in the case of 2 children, both with tuberculous cervical adenitis (tubercle bacilli found). Wasting and fever developed after a few weeks of treatment, which was discontinued; shortly afterwards the glands became smaller and search for bacilli proved negative. Two adults with tuberculous epididymo-orchitis were treated for 6 months; the testes became smaller and painless. In 2 cases of empyema in which thoracoplasty had failed, vitamin D_2 also failed to affect suppuration. Twelve cases of bone and joint tuberculosis were treated; 8 improved (weight increased, fistulae healed, arthritis less), 3 remained stationary, and 1 got worse. Great improvement was found in 3 out of 4 cases of tuberculous laryngitis. Of the 33 cases with pulmonary tuberculosis, the condition was very advanced in 17, and moderately so in 16. None had improved with collapse therapy. The majority of radiographs showed that after calciferol treatment either new cavities had formed or old ones were larger.

It is concluded that intensive calciferol therapy gave good results in children with cervical adenitis, and in most adults with bone and joint conditions; tuberculous laryngitis appeared to respond well, but pulmonary tuberculosis responded badly. *T. E. C. Early*

2285. **Treatment with Antireticular Cytotoxic Serum in Pulmonary Tuberculosis**
H. R. NAYER. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **57**, 489–494, May, 1948. 13 refs.

Ten patients with advanced progressive pulmonary tuberculosis were treated with antireticular cytotoxic serum. During follow-up periods of 4 months, no beneficial effects were observed. In 1 patient, a harmful effect could be ascribed to the use of the serum.—[Author's summary.]

2286. **Streptomycin Treatment of Tuberculous Meningitis**
STREPTOMYCIN TRIALS COMMITTEE, MEDICAL RESEARCH COUNCIL. *Lancet* [*Lancet*] **1**, 582–596, April 17, 1948. 2 figs., 14 refs.

This report comes from the Streptomycin Trials Committee of the Medical Research Council and summarizes results in 105 cases of tuberculous meningitis treated at a number of centres. Of these 92 are analysed in this report. In all the cases diagnosis was confirmed by culture, guinea-pig inoculation, or necropsy, and the survivors underwent a minimum of 120 days' observation.

The streptomycin used was the hydrochloride obtained from one producer. The condition of each patient on admission was classed as "early", "advanced", or "medium" on clinical data; broadly, response to treatment was more favourable in the early cases. That in many children under 3 years the disease was in an advanced stage partly explains the bad prognosis at this age. As regards lesions additional to meningitis, 27% had miliary lesions in the lungs, 25% one or both elements of the primary complex, and 13% other lesions in lung, bone, or skin. The presence of miliary or recent primary lesions seemed to worsen the prognosis. All factors in diagnosis of the meningitis were investigated. The finding of a low sugar content in the cerebrospinal fluid (C.S.F.) assisted diagnosis from benign lymphocytic meningitis. The value of the Mantoux test is emphasized.

After an initial period in which dosage was too high, the dose was stabilized at 0·02 g. per lb. (0·45 kg.) body weight intramuscularly over 24 hours and 0·05 g. to 0·1 g. intrathecally in 5 to 10 ml. of normal saline once daily. On this dosage toxic effects were unimportant, but streptomycin appears to be irritant to the meninges when given intrathecally (as shown by a C.S.F. pleocytosis). Because of this, after June, 1947, alternate patients had intramuscular injections alone, but it was found that results were considerably better with combined therapy (78% of 28 patients receiving intramuscular injections alone and 58% of 72 given combined treatment died). Figures are given in the following tables.

TABLE 1
Results of Streptomycin Treatment Related to Age

Age (yrs.)	No. of Cases Admitted before Aug. 18, 1947	Condition on Dec. 15, 1947			
		Good	Stationary or Relapsed	Deteriorating	Dead
Under 3 ..	33	4 (12%)	0	2 (6%)	27 (82%)
3 to 5 ..	26	10 (38%)	2 (8%)	0	14 (54%)
6 to 8 ..	25	11 (44%)	3 (12%)	0	11 (44%)
9 and over	21	5 (24%)	1 (5%)	0	15 (71%)
All ages ..	105	30 (28%)	6 (6%)	2 (2%)	67 (64%)
On March 15, 1948	105	27 (26%)	6 (6%)	1 (1%)	71 (67%)

TABLE 2
Results of Combined Intrathecal and Intramuscular Streptomycin Treatment in Children of 3 Years and Over and Adults

Stage of Disease on Admission	No. of Cases Admitted before Aug. 18, 1947	Conditions on Dec. 15, 1947		
		Good	Stationary or Relapsed	Dead
Early ..	15	9 (60%)	2 (13%)	4 (27%)
Medium ..	21	9 (43%)	1 (5%)	11 (52%)
Advanced	12	3 (25%)	0	9 (75%)
All stages	48	21 (44%)	3 (6%)	24 (50%)
On March 1948 ..	48	19 (40%)	3 (6%)	26 (54%)

The scheme of treatment varied in the different centres. "It was found that in the centre where the least intrathecal treatment was given and where all streptomycin treatment was interrupted frequently and for relatively

long periods, the highest proportion of good results was obtained." Daily intrathecal treatment over a long period was probably even harmful. Intrathecal injection produces very high levels of streptomycin in the C.S.F. and intramuscular injections alone much lower levels, but in the latter case levels were higher when the meningitis was intense or progressive. It is hinted that low levels in the C.S.F. are probably bacteriostatic but that higher levels may be needed for bactericidal effect. In many who ultimately died life was prolonged but even in cases which responded late relapses were possible. The explanation of relapses is not obvious. Late thrombosis of cerebral vessels explains 1 or 2 only, and apparently in only a small proportion of cases (3 of 22 tested) resistant strains of bacilli developed. "The persistence and breakdown of foci of infection inaccessible to circulating streptomycin may well be an important factor." Spinal block was diagnosed clinically in 20 of 92 cases, and it appeared to resolve spontaneously in 4, 2 of which did well. In a majority of all cases, after 3 weeks the C.S.F. became free of tubercle bacilli for long periods, but in patients who ultimately did badly the bacillus was found much more frequently during the first 3 weeks than in those who did well. The effect on lesions in other organs than the meninges was interesting. Many miliary foci improved, but it was possible for active tubercles to appear during treatment and active primary complexes did not seem to be affected.

[The original article must be consulted for case details and for recommended procedures. It is a very valuable contribution.] *J. V. Hurford*

2287. **Treatment of Tuberculous Meningitis with Streptomycin. A Report to the Medical Research Council**
H. V. SMITH, R. L. VOLLUM, and H. CAIRNS. *Lancet* [*Lancet*] **1**, 627–636, April 24, 1948. 8 figs., 8 refs.

The results are reported of streptomycin treatment of 18 cases of tuberculous meningitis at the Radcliffe Infirmary, Oxford, since November, 1946. Absolute confirmation of the diagnosis was obtained in 15 cases. Of the patients, 7 died (life prolonged in 5); of the 11 survivors 7 had streptomycin for 68 to 255 days and 1 to 6 months later are without symptoms. The remaining 4 are still under treatment. There were 4 children under 5 years of age, 1 child aged 7, 2 patients between 10 and 15, 5 between 15 and 20, and 6 between 20 and 25. In most of the cases, streptomycin was given by intramuscular (adults 2 g. daily, and infants 0·02 g. per lb. body weight daily) and intrathecal (0·1 g. in adults, 0·05 to 0·75 g. in infants) injection for at least the first 6 weeks and then for 4 to 6 months by intramuscular injection alone (single dose of 2 g.). The intrathecal injection was into the lumbar subarachnoid space, anterior horn of lateral ventricle, or, occasionally, into the subarachnoid space in the region of the optic chiasma. As there was one instance of pyogenic superinfection, emphasis is placed on sterile precautions.

In fatal cases, the most intense tuberculous changes were found in the cisterna ambiens, the interpeduncular space, and the proximal part of the Sylvian fissures. The arteries of the circle of Willis were usually embedded in exudate and one or other was sometimes thrombosed. The clinical results of these changes included communicating hydrocephalus, cerebral anoxia or infarction, and symptoms of hypothalamic disturbance. Some degree of hemiplegia, usually of faciobrachial type, was common. Spinal block occurred in 4 cases.

Much of the interest from this report is derived from the less usual procedures which were tried. Study of the lateral ventricles through frontal burr-holes (16 cases) was an aid to diagnosis (differentiation from brain abscess and finding of the tubercle bacillus more easily than by lumbar puncture), to estimation of hydrocephalus by ventriculography, and to treatment (streptomycin administration in spinal block, relief of acute pressure). Streptomycin was introduced into the region of the interpeduncular space in 4 cases, through a frontal flap with 5 "polythene" tubes passed towards the Sylvian fissures and above the diaphragma sellae; the method may be of value where disease is advanced when the patient is first seen. Continuous ventricular drainage and irrigation from lateral ventricle to lumbar space were tried and abandoned.

The authors argue against facile abandonment of treatment. "In all our adult patients who ultimately recovered completely, hemiparesis and dementia with periods of stupor persisted for many weeks: they were disorientated, inattentive, incontinent, difficult to feed, with gross failure of memory." Of the 7 survivors who have completed treatment, the neurological recovery is complete except for loss of caloric response and high-tone deafness in the adults, the behaviour of all is normal, and in 6, tested psychometrically, intellectual recovery appears full, except perhaps for slightly slowed response. *J. V. Hurford*

2288. **The Use of Intrathecal Heparin in Conjunction with Streptomycin in the Treatment of Tuberculous Meningitis. Preliminary Report**
C. A. ST. HILL, C. RILEY, and J. H. GIFFORD. *Journal of Clinical Pathology* [*J. clin. Path.*] **1**, 157–161, May, 1948. 6 figs., 3 refs.

One of the commonest causes of failure in the treatment of tuberculous meningitis by streptomycin is the formation of intracranial and intraspinal adhesions. These are produced partly as a result of fibroblastic reaction around tuberculous foci, but their inception and growth may well be stimulated by the deposition of fibrin from the cerebrospinal fluid, which is rich in fibrinogen in this condition. If fibrin deposition could be prevented, the formation of adhesions might be lessened and the prognosis improved. Heparin is the obvious drug for this purpose.

This paper deals with the effect of mixing heparin and streptomycin, and of giving heparin intrathecally to a patient receiving streptomycin. When a solution of heparin is added to one of commercial streptomycin a precipitate forms which contains heparin but not streptomycin. If, with ordinary commercial heparin, the amount is less than two-thirds of the streptomycin no heparin is left in the supernatant fluid; if more heparin

is added, active heparin begins to appear in the supernatant fluid. By the addition of enough heparin, concentrations of 1,000 units per ml. or over can be obtained. No streptomycin is contained in the precipitate, and it was concluded, therefore, that the precipitate was caused by impurities in the streptomycin. On the other hand, if a very pure sample of heparin is used very little precipitation occurs at all. If further streptomycin is added to supernatant fluid containing heparin and streptomycin there is no further precipitation; this mixture can be given intrathecally without ill effect.

When ordinary heparin was given intrathecally to a patient receiving intrathecal streptomycin, there was a marked reaction, with stiff neck and a sharp rise in the cellular and protein content of the cerebrospinal fluid. Heparin can be administered to a patient receiving only intramuscular streptomycin without any reaction, thus confirming the view that the impurities in the streptomycin cause the precipitation. By these procedures heparin can be introduced regularly into the theca of patients receiving streptomycin treatment. The effect of this on prognosis has yet to be investigated. The authors emphasize the need for assaying the heparin content of all heparin–streptomycin mixtures before use.

N. S. Alcock

2289. **Treatment of Miliary Tuberculosis and Tuberculous Meningitis with Streptomycin, Sulphone [" Promin "], and Vitamin A.** (Terapie della tubercolosi con streptomicina, solfone e vitamin A. (Tubercolosi miliare e meningite tubercolare))

C. Cocchi. *Rivista di Clinica Pediatrica* [*Riv. Clin. pediat.*] **46**, 209–275, April, 1948. 59 figs., bibliography.

The technique recommended for treating miliary tuberculosis and tuberculous meningitis consists of administration of " promin ", streptomycin, and vitamin A. Five 4-hourly injections of streptomycin, 0·07 to 0·11 g., are given daily, that is, 0·35 to 0·6 g. in 24 hours. An adult or large child receives 0·01 g. per kilo per day, a small child 0·02 g. per kilo, and an infant 0·03 g. per kilo. Three courses of 25 days each are given, with 5 days' rest between courses. In most cases treatment is then stopped. Usually 3 g. of promin, *p,p'*-diaminodiphenylsulphone-N,N'-didextrose sulphonate (for smaller children 1·5 g.), is given by intravenous injection at the same time and for the same periods as streptomycin. In some recent cases the sulphone has been given by mouth in doses of 0·04 g. per kilo per day, divided into 3 or 4 doses, the lesser dose being given because of the readier breakdown into the parent sulphone, and therefore greater toxicity, when given by mouth. If toxic symptoms occur (cyanosis, vomiting, abdominal upsets, anaemia) the sulphone is given in lower doses after a pause of a few days. On alternate days for 15 to 30 weeks 50,000 units of vitamin A are also given. In cases of tuberculous meningitis, streptomycin is also given intrathecally in doses of 0·05 g. for an adult and 0·03 g. for a child. After the acute stage, smaller doses—down to 0·015 g.—are often sufficient. Infants receive 0·015 g. from the beginning. Successive courses are given: (1) daily for 25 to 40 days; (2) on alternate days for 20 to 30 days; (3) after a rest for 3 to 4 days (during which spinal fluid is examined), every 2 to 3 days for 30 to 40 days; (4) after another rest and lumbar puncture, every 2 to 4 days for 30 to 40 days. When the cerebrospinal fluid is " almost normal " another pause is made for 10 days. Finally streptomycin is given every 6 to 10 days for several weeks.

Twenty-nine cases of miliary tuberculosis were treated. Streptomycin given by the author's method " always cures the patient, and the patient is permanently and definitely cured ". [Examination of the figures hardly bears out this exciting assertion: Of 16 patients without meningitis 1 died in 6 days. Thirteen developed meningitis, 5 during treatment; 1 of these died and 1 remained gravely ill. Eight were admitted with miliary tuberculosis and meningitis; 2 of these died and the other 6 were still under treatment. No criteria of diagnosis are given and no follow-up period is mentioned; it appears that some, at least, of those " cured " are still under treatment.] In 107 cases of tuberculous meningitis a mortality of only 37% is claimed. In the period Aug., 1947, to March, 1948, when daily rather than intermittent intrathecal administration of streptomycin was used, the mortality is said to have fallen to 16%. [With considerable difficulty a more accurate analysis can be extracted from the author's tables and diagrams. Of 55 patients admitted from Dec., 1946, to July, 1947, with follow-up to April, 1948, 14 were " cured " and had finished treatment for 4 months or more; 6 were " cured " and had finished treatment for less than 4 months; 33 had died; 2 were still under treatment. Of 52 patients admitted from Aug., 1947, to March, 1948, with follow-up to April, 1948, 20 were " cured " and had finished treatment for 3 weeks or more; 8 had died; 17 were improving, but still under treatment; 7 were still acutely ill. Both these lists exclude those dying within " the first few days ". In the first group 9 out of 55 died within 8 weeks of starting treatment, in the second group 6 out of 52. This suggests that further follow-up may show little difference in mortality between the 2 groups. The low over-all mortality claimed by the author is obtained by excluding deaths occurring within the " first few days " and including as survivors all cases still alive, even those admitted up to 3 weeks before publication. The adjusted mortality is much the same as that obtained elsewhere with streptomycin alone. In spite of the exaggerated claims made for this method of treatment, the relatively successful results obtained with small doses of streptomycin, in association with a sulphone, merit attention and further investigation. Lack of space prevents an abstract of many other points of interest in this long and detailed paper.]

John Crofton

See also Section Pharmacology, Abstract 2004.

2290. **Serous Tuberculosis in East African Natives**

S. R. Wood. *British Journal of Tuberculosis* [*Brit. J. Tuberc.*] **42**, 38–45, April, 1948. 9 refs.

This paper is concerned with observations made on 169 African negroes aged 18 to 30 who were treated at

the East African Command Chest Centre between 1944 and 1946. Sixteen patients had primary lymph node tuberculosis complicated by a pleural effusion. The effusion developed at the beginning of the illness in 7 and after an interval of some 3 months in 9. The illness was prolonged but benign, and enlargement of hilar lymph nodes persisted for many months. In 125 patients there was a primary unilateral pleural effusion, which in 55% was right-sided. The onset was acute in 20%, subacute in 60%, and insidious in 20%. The fluid was clear, and usually showed a predominance of lymphocytes; in some cases it contained more than 4% protein, was sticky, and tended to clot spontaneously. The supraclavicular lymph nodes were enlarged sometimes, considerably in 12%. After resolution appreciable pleural thickening remained in 70%.

In 28 patients there was an incomplete or total polyserositis. In 11 an initial unilateral pleural effusion was followed in 3 to 18 months by an effusion on the opposite side and in 3 cases by a pericardial effusion. Absorption of the fluid with arrest of the disease occurred in 10; 1 died of miliary disease. In 17 cases typical polyserositis developed with 4 deaths from miliary spread. These observations are characteristic of primary tuberculosis in adult negroes. In contrast with the lesions in adult Europeans, a unilateral pleural effusion often complicates a primary lymph node syndrome or initiates a polyserositis. *Arthur Willcox*

2291. **Retrogression of Tuberculous Skin Manifestations in Progressive Pulmonary Tuberculosis.** (Zur Rückbildung tuberkulöser Hauterscheinungen bei progredienter Lungentuberkulose)
K. W. KALKOFF and F. EHRING. *Strahlentherapie* [*Strahlentherapie*] **77**, 359–370, 1948. 1 fig., 15 refs.

Two patients with pulmonary tuberculosis who also suffered from lupus vulgaris showed a marked change in their condition shortly before death. There was a sharp deterioration in their general condition, associated with progressive lung and intestinal lesions and with coincident spontaneous healing of the skin affection. At the same time they lost weight and there was a fall in the red cell count, in the white cell count, and in sensitivity to tuberculin. The authors discuss the possibility of the existence of an active protective influence, arising from a lesion in the skin or possibly elsewhere. Two further cases are cited of Boeck's sarcoid in which, coincidentally with healing of the skin lesions, progressive pulmonary tuberculosis developed. The case histories are given in detail. *W. J. Czyzewski*

2292. **The Inhibitory Action of the Monoethyl Esters of S-*n*-Alkylthiomalic Acids and the Monoethyl Esters of Alkane Sulphonyl Succinic Acids on the Growth of *Mycobacterium tuberculosis***
P. A. MCNALLY. *Journal of Hygiene* [*J. Hyg., Camb.*] **46**, 60–61, March, 1948. 4 refs.

In an earlier paper (*Brit. J. exp. Path.*, 1947, **28**, 161) the author had demonstrated that various half-esters of monoalkyl succinic acids inhibited growth of *Mycobacterium tuberculosis*; other workers had shown that certain sulphone compounds were well known to be active against this species. The author therefore tested the effect *in vitro* of mono-ethyl—that is, half—esters of alkylthiomalic (alkylthiohydroxy-succinic) acids and of the corresponding alkane sulphonyl succinic acids obtained therefrom by oxidation. The length of the alkyl chain varied from C_9H_{19} to $C_{18}H_{37}$. These compounds were moderately tuberculostatic, but they were also strongly lytic to suspensions of washed red cells; the degree of both effects varied with the length of the alkyl chains. Both antibacterial and haemolytic activities were reduced in the presence of human serum. *P. D'Arcy Hart*

CHOLERA

2293. **A New Technique for Preparation of Anticholera Vaccine.** (Una nueva técnica de preparación de vacuna anticolérica)
E. SUÁREZ PEREGRÍN. *Actualidad Médica* [*Actualid. méd., Granada*] **24**, 197–199, April, 1948.

The author does not claim that the method he describes is original, but that the process is valuable in laboratories with limited equipment and worthy of extended trial. The organism—that is, *Vibrio cholerae*—is cultivated in a liquid medium and the entire material used for inoculation, after the organism has been killed. The medium must be isotonic, neutral, or slightly alkaline, and colourless or nearly so; it must be such that after 48 hours' incubation the culture will be of the strength ready for inoculation (for *V. cholerae*, 8,000 million per ml.). The medium must be free from irritant or sensitizing substances, and an antiseptic must be chosen which will not lower the antigenic potency or cause lysis of the organism.

After a series of trials it was decided to avoid employment of meat, broth, meat extracts, albumins, or peptones and to use amino-acids. Hydrolysed casein proved to be an excellent medium and it was found that a dilution of 1 part with 4 parts of physiological saline gave the desired strength of growth (8,000 million *V. cholerae* per ml.). Other dilutions would probably be needed for other organisms, according to the strength required. The antiseptic chosen was formol, so that anavaccine was produced. The product was kept at 37° C. for a certain time to detoxicate it and also to make it less irritant by driving off part of the formol.

The procedure in detail is as follows: (1) Hydrolysed casein, 200 ml. and normal saline 800 ml. are neutralized with normal NaOH to *p*H 7·6, sterilized for 15 minutes at 120° C., and incubated for 24 hours at 37° C. to prove sterility. (2) Seeding is carried out with a loopful of 48-hour culture with subsequent incubation at 37° C. for 48 hours. (3) Formol is added (40% formic aldehyde) to a strength of 0·4%. (4) Detoxication and partial elimination of the formol is achieved by keeping at 37° C. for 8 days. The vaccine is then tested for sterility and titrated for strength.

In the case of cholera, if the above technique is carried out, there is no need for titration; the product is of the strength desired, and it is not glairy or mucoid. *H. Harold Scott*

2294. **Some Observations on the Effect of Cholera Vaccine During the Recent Cholera Epidemic in Egypt**
A. H. KORDI. *Journal of the Royal Egyptian Medical Association* [*J.R. Egypt. med. Ass.*] **31**, 289–299, April, 1948. 1 fig.

The author has studied the effects of cholera vaccine on 430 cases of cholera, the diagnosis being mainly made from bacteriological examination, but in a few cases solely on clinical grounds. Vaccination was not uniform, some patients receiving a single dose of 1 ml. of vaccine, others doses of 0·5 and 1 ml. with a week's interval. Among 281 patients not vaccinated the death rate was 24·55%, among 78 vaccinated less than 7 days before the onset it was 12·8%, and among 71 vaccinated more than 7 days before the onset 5·6%. Presumably some of those in the last group had received 2 doses. The mortality rate for those given a single dose of vaccine was 9·8%, and for those given 2 doses 8·1%.

In about half of 250 convalescent carriers examined bacteriologically daily, vibrios began to disappear within 7 days, the longest time of excretion being 33 days. Among 2,037 contacts 84 were found to be healthy carriers, all the latter ceasing to carry vibrios within 15 days. Vaccination appeared to lessen the risk of becoming a carrier but to have no effect on the duration of the condition. It lessened the mortality in cholera especially if given in 2 doses 7 or more days before the attack and conferred a degree of immunity, the incidence in the non-vaccinated being 3·9 times greater than that in the vaccinated. [Some of the tables and statistics are a little confusing.] *C. F. Shelton*

2295. **Clinical Study of 689 Cases of Cholera Isolated in the Abbassia Fever Hospital**
A. H. EL-RAMLI. *Journal of the Royal Egyptian Medical Association* [*J.R. Egypt. med. Ass.*] **31**, 322–350, April, 1948.

Over a period of 2 months 689 cases of cholera were admitted to hospital, the stools in most containing typical cholera vibrios. In the remainder there were clinical signs and symptoms; in fatal cases signs of the infection were always found at necropsy. Females were less affected than males, while 50% were in the age group 20 to 35. Nearly all patients were of low social standard, with a few exceptions, in all of whom attacks were mild. Characteristic symptoms were diarrhoea, vomiting, and dehydration, the onset being almost always sudden and diarrhoea being present in nearly 98% of cases. Of 325 patients specially investigated severe dehydration was found in 38·2%. The blood specific gravity varied from 1,050 to 1,078 (normal for Egyptians being 1,054 to 1,058). After hydration the general condition improved and recovery was usually quick; 65% of patients were afebrile, and hyperpyrexia was not met with. Twelve ambulatory cases were found accidentally. The blood urea, estimated in 52 cases, was always above the normal before hydration, improvement being rapid as blood urea decreased. Complications included abortion (11 out of 14 pregnancies), corneal ulcer, pneumonia, and pulmonary oedema.

In 209 cases stools were positive, in 76% in the first 4 days of illness, and in 91% within 7 days of onset; by the thirtieth day 99·6% were negative. Among 2,035 contacts 84 healthy carriers were found, the longest duration of the carrier state being 15 days. Some 56·3% of patients died within 24 hours of admission, but a large proportion of these were brought in dead, the most important causes of death being dehydration, circulatory failure, and uraemia. Other factors influencing prognosis were age (mortality is lowest in the age group 5 to 20 years), pregnancy (of 14 pregnant women 5 died), high blood urea, and vaccination (the mortality rate was 7·6% in the vaccinated as against 17·3% in the non-vaccinated). Vaccination at onset or during the first 3 days of illness had no beneficial effect. Those who arrived at hospital dead or moribund or who died within the first 5 hours of admission are excluded from a death rate given as 12·7%. [The mortality figures are given in rather a confusing way.]

Patients with a blood specific gravity not above 1,060 did not usually require parenteral fluids, but 400 ml. of normal saline was given intravenously for every degree above this figure, at the rate of about a litre an hour. In advanced dehydration fluid was given more rapidly. Signs of relapse after hydration should be watched for. In some cases when the blood specific gravity was 1,060 or less signs of dehydration were evident and intravenous saline was needed. Blood pressure is an important guide to treatment; when it is very low parenteral saline must be given rapidly. In the latter part of the epidemic 40 g. of sodium bicarbonate was added to every litre of saline, the solution being passed through a Seitz filter. In some cases 100 to 200 ml. of 50% glucose was given intravenously daily, or 5% glucose subcutaneously or intravenously by drip. Analeptics were of no benefit but atropine was useful in cramp and pulmonary oedema. The digitalis group of drugs were valuable in congestive heart failure, and pituitrin was also of use. Sulphonamides were not found to be of value. Sodium phthalylsulphacetamide had no action on the condition in patients or carriers.
C. F. Shelton

2296. **The Viability of Pathogenic Intestinal Organisms in Sea Water with Special Reference to *Vibrio cholerae***
M. A. GOHAR, A. ELYAN, M. MAKKAWI, A. EISSA, and A. BASHATLY. *Journal of the Royal Egyptian Medical Association* [*J.R. Egypt. med. Ass.*] **31**, 358–372, April, 1948. 3 figs., 2 refs.

Alexandria discharges its sewage directly into the sea through a pipe about 500 metres long. Samples of sea water were taken from the sewage effluent itself, from water at the site of disposal, and from various places along the neighbouring coast up to a distance of 12 miles (19·2 km.) from the sewage pipe. Samples were also taken at Suez, Port Said, Ras-el Bar, and Damietta. Specimens of the cleanest and dirtiest sea water were artificially contaminated with cholera vibrios by adding to every litre of water 5,000 million organisms from a saline suspension washed from a 24-hour agar culture of *Vibrio cholerae*. In addition varying dilutions

of sewage contaminated with cholera vibrios were added to some of the cleanest samples of sea water.

The authors consider that discharge of sewage into the sea results in many cases in an unsatisfactory bacteriological condition of the water near the disposal sites. The life of cholera vibrios and other pathogenic organisms in ordinary sea water is a short one, this being considered to be due to the presence of a bactericidal agent of undetermined nature, whose action is probably enhanced by the growth of saprophytic organisms. This agent is thermolabile, gradually loses its potency at room temperature, and is completely inactive after about a month. It is probably constantly renewed under natural conditions. It is considered that the chief danger of sewage disposal in sea water lies in shell-fish infection.

C. F. Shelton

PROTOZOAL INFECTIONS

2297. **The Pathology of an Experimental Amoebic Infection in the Rat**

G. T. Stewart and W. R. Jones. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **42**, 33–45, April, 1948. 10 figs., 36 refs.

Young rats were infected by intracaecal inoculation of *Entamoeba histolytica* by the method described by Jones, 1946 [see *Abstracts of World Medicine*, 1947, **1**, 449].

With two strains of amoebae the infectivity, as measured by the proportion of rats infected, was correlated with the virulence, as measured by the severity of the lesions produced. A third strain showed high virulence in all experiments and there was no significant correlation with infectivity. The infectivity of this strain was also high, the lowest figure obtained in 18 experiments being a proportion of 60% infected. The severity of lesions was not correlated with the number of organisms injected.

Histological preparations of the caecum showed the amoebae to be invading the mucosa within 24 hours of inoculation. The lesions were of two types: (*a*) erosions with the formation of small follicular ulcers full of amoebae and mucus, but with little inflammatory reaction; (*b*) larger lesions with congestion and leucocytic infiltration of the mucosa. The latter type predominated when virulent bacteria were added to the inoculum. At later stages, the changes included widespread inflammation and oedema, mucus secretion, and desquamation of the mucosa. Sometimes there was localized peritonitis with adhesions, but amoebae were only rarely observed in the deeper layers of the bowel wall. Healing usually began after 7 days.

Aerobic cultures of caecal contents upon certain media —horse blood, McConkey, desoxycholate citrate, bismuth sulphite agar, and blood agar with 0·1% sodium azide—showed that infection with amoebae had little effect upon the nature of the bacterial flora. In 6 of 37 infected animals non-lactose-fermenters became predominant; these organisms were present in small numbers in 9 of 42 normal rats. No anaerobic cultures were made.

Strains of *Bacterium coli* and the paracolon bacillus (group I), in doses of 10 to 1,000 million bacteria, administered by mouth to normal rats, caused only slight hyperaemia of the gut; when given to rats infected with amoebae the severity of the lesions was significantly greater than in control animals. The strain of paracolon bacillus used was identified in the caecal contents. *Shigella flexneri* is stated to have " failed appreciably to aggravate the infection " and the organism could not be recovered from the gut. [The tables show that the average severity of the lesions was increased by *Sh. flexneri* and by paracolon bacillus to about the same extent. With paracolon bacillus, 83 rats and 69 controls were used, and the difference was significant; with *flexneri* 8 rats and 11 controls were used, and because the numbers were small, the same difference was not significant.]

Doses of phthalylsulphathiazole (500 mg. per kilo of body weight orally) or penicillin (500 units subcutaneously) given on 4 occasions during the 48 hours preceding inoculation reduced the proportion of rats infected and the severity of the lesions. When both drugs were administered, the effect was greater than with either given alone. As neither drug showed amoebicidal activity *in vitro* it is concluded that the action was to prevent or reduce the secondary bacterial infection. Penicillin also had some effect upon established amoebic infections; phthalylsulphathiazole enhanced this effect, although it was inactive alone.

The authors consider that the initial infection with a strain of amoebae depends upon its intrinsic invasive power, but that the severity of the lesions is influenced profoundly by bacteria, which produce secondary infection and inflammation at the sites of amoebic invasion. [This is a useful concept, but no real evidence is presented to show that amoebae differ in intrinsic invasive power. If this were so, the proportion of animals infected would be to some extent independent of variations in the lesions brought about by administration of virulent bacteria or protective drugs. In all the experiments recorded here, every increase or decrease in severity of infection is accompanied by an increase or decrease in the proportion of animals infected.] *L. G. Goodwin*

See also Section Hygiene and Public Health, Abstract 1946.

2298. **A Note on the Effect of High Temperature on the Pupal Stage of *Glossina* in Relation to the Transmission-rate of Trypanosomes**

T. A. M. Nash. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **42**, 30–32, April, 1948. 6 refs.

In Burtt's experiments (*Ann. trop. Med. Parasit.*, 1946, **40**, 18; **41**, 50) tsetse flies (*Glossina morsitans*), which hatched from pupae incubated at about 86° F. (30° C.), showed a greater transmission rate for *Trypanosoma rhodesiense* than those hatched from pupae kept at the lower average temperature of the laboratory. In Northern Nigeria, Nash (*Bull. ent. Res.*, 1942, **32**, 327) found many pupae of *G. submorsitans* in soil at temperatures ranging from 69° to 82° F. (20·5° to 28° C.) but

very few at higher temperatures, and as the shade temperature reached 106° F. (41·1° C.) it is probable that Burtt's pupae were incubated at a higher temperature than they would experience in nature; his experiments should be repeated at 69° and 82° F.

The author's work in Nigeria (*Bull. ent. Res.*, 1937, **28**, 75; 1939, **30**, 259) led him to conclude tentatively that most sleeping sickness conveyed by the riverine tsetse flies *G. palpalis* and *G. tachinoides* is contracted in the late dry season when the soil temperature is high and when the flies have become restricted to permanent water pools, such as the village water holes; here contact between the flies and the people is close, and the flies are compelled to feed largely on human beings. Confirmatory evidence for this view was not obtained from the dispensaries, because the disease is mild in character and natives present themselves late for treatment. If it should be confirmed it may be possible to reduce the length [and cost] of protective clearings of river crossings to that required for the dry season only. *J. F. Corson*

2299. **The Action *in vitro* of Some Aromatic Diamidines on a Sudan Strain of *Leishmania infantum***
S. ADLER, I. TCHERNOMORETZ, and M. BER. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **42**, 1–4, April, 1948. 12 refs.

Two strains of leishmania were investigated: an Indian strain of *Leishmania donovani* and a Sudanese strain which, because of its relative resistance to treatment in man, the authors prefer to regard as a strain of *L. infantum*. Tubes containing the diamidines dissolved in 5 ml. of Locke–serum–agar were inoculated each with 2,000,000 flagellates and incubated at 24° C. Other series of tubes were left for 24 or 48 hours at 37° C. before incubation at 24° C. The numbers of living flagellates per c. mm. were counted at the end of the experiment, and the concentration of drug which just allowed the survival of a few flagellates without multiplication was determined.

Similar experiments were carried out with suspensions of leishmania forms from infected hamsters. The leishmania were enumerated by mixing with a standardized suspension of fowl erythrocytes and counting the relative numbers of parasites and cells in stained smears. Pure penicillin (5 units per c. mm.), which had no effect upon leishmania, was added to the medium to ensure sterility. Propamidine and pentamidine were more active against the Indian than against the Sudanese strain. Stilbamidine was less active than the other two drugs, but was equally potent against both strains. Leishmania forms were more susceptible than flagellates, but concentrations of drug which just prevented multiplication did not cause permanent damage to the organisms, which exflagellated and multiplied when transferred to fresh medium. The effective concentrations of drugs were higher than those observed by Collier and Lourie (*Ann. trop. Med. Parasit.*, 1946, **40**, 88) [who used a clear, fluid medium composed of rabbit serum and laked rabbit cells free from agar and particles which might adsorb the drugs]. *L. G. Goodwin*

MALARIA

2300. **Sternal Puncture and Malaria**
J. K. MEHTA. *Indian Physician* [*Indian Physician*] **7**, 90–95, April, 1948. 2 refs.

Sternal puncture for the diagnosis of malaria was performed in 175 cases (174 of them in males). Films from both the marrow and the peripheral blood were stained with dilute Giemsa and carefully examined. No extracellular forms of parasites were recognized as diagnostic. Of the total number of cases parasites were present in 83, in the peripheral blood and sternal marrow in 64, and in the sternal marrow alone in 19. Parasites were sometimes found in the peripheral blood only after a very prolonged search, whereas in the sternal smears they were often found after a few minutes' examination. *Plasmodium falciparum* crescents and ring forms and *P. vivax* trophozoites were found in smears. Some of the cases were clinically atypical, but pyrexia and a palpable spleen were present in the majority. Two cases of cerebral malaria were seen, both with parasites in the peripheral blood and in sternal smears. One of these patients recovered after intramuscular quinine, the other died in spite of intensive treatment with this drug, about gr. 50 (3·2 g.) of quinine being given daily —gr. 30 intramuscularly and gr. 20 by stomach tube. [Apparently intravenous medication with quinine and/or mepacrine was not used.] Six patients in the present series recovered without quinine (5 benign tertian and 1 malignant tertian) and after a month had had no relapse.

[Sternal puncture would appear to be of value in doubtful cases where parasites cannot be found in the peripheral blood and in the very early stages of malignant tertian malaria.] *C. F. Shelton*

2301. **Tissue Forms of a Malaria Parasite. *Plasmodium cynomolgi***
F. HAWKING, W. L. M. PERRY, and J. P. THURSTON. *Lancet* [*Lancet*] **1**, 783–789, May 22, 1948. 13 figs., 18 refs.

After giving a short history of the search for the exo-erythrocytic (tissue) forms of malarial parasites of birds and mammals carried out in different countries during the last 10 to 15 years, the authors describe their own investigations of experimental infections of rhesus monkeys (*Macaca mulatta*) with *Plasmodium cynomolgi*, a parasite of monkeys closely resembling *P. vivax*, the cause of benign tertian malaria. Shortt *et al.* showed recently that the tissue forms of these two species of parasites occur in the liver (*Nature*, 1948, **161**, 126; *Brit. med. J.*, 1948, **1**, 192 and 547). The numerous experiments recorded in this paper were carried out at the National Institute for Medical Research, Hampstead, London. Rhesus monkeys were infected with *P. cynomolgi* by injection of sporozoites in salivary glands of infected *Anopheles quadrimaculatus* and *A. maculipennis* into the blood stream, skin, and various organs; observations were made during 9 days after injection.

Subinoculation of minced liver 2 days, 5 days, and

7 days 15 hours after injection of sporozoites did not produce infection though parasites were found (later) in material removed from the livers in the last two periods. Subinoculation of several other tissues—spleen, lung, skin, marrow, cerebrum—also failed to infect monkeys. Blood was removed at various periods after injection of sporozoites and was injected intravenously into monkeys; it was not infective until 7 days 21 to 23 hours later when, presumably, merozoites began to enter the blood from the liver. Experiments showed that this entry of merozoites is continuous for at least 48 hours; it was calculated that in infections from a few mosquitoes about a million parasites enter the blood from the liver, while in infections from 100 mosquitoes the numbers would be from 100 to 1,000 million. In one experiment a tourniquet was placed round the monkey's arm, sporozoites were injected intradermally in the hand, and after 2 hours 0·7 ml. of venous blood was taken distally to the tourniquet, and inoculated into a monkey; both the donor and recipient monkey became infected. Tissue cultures of portions of spleen, lymph nodes, and bone marrow from sites previously inoculated with sporozoites did not reveal parasites; liver cells failed to grow in cultures.

The authors describe in detail, with illustrations, the appearance of the parasite in liver sections at 5 days, 7 days 15 hours, and 7 days 23 hours after inoculation of sporozoites.

A monkey was inoculated intracerebrally with sporozoites and showed blood infection after 17 days; 7 days 8 hours after inoculation the site was examined and one tissue form of parasite was found in sections of the grey matter.

These findings confirm those of Shortt *et al.*; the earlier stages of development of the sporozoites in the monkey are not yet known. The authors refer to similar developmental forms of *Hepatocystes* (*Plasmodium*) *kochi* (Garnham, *Trans. R. Soc. trop. Med. Hyg.*, 1948, **41**, 601) and other parasites, and discuss certain views on the evolution of this group of protozoa and the significance of the tissue forms of *P. vivax* in the human liver.

J. F. Corson

2302. **Curative Action of Pamaquine Naphthoate, Quinacrine Hydrochloride, and Quinine Bisulphate in *Plasmodium cathemerium* Infections of the Duck**
H. A. WALKER, L. A. STAUBER, and A. P. RICHARDSON. *Journal of Infectious Diseases* [*J. infect. Dis.*] **82**, 187–196, March–April, 1948. 3 figs., 5 refs.

A method of comparing antimalarial drugs in respect of their curative and suppressive action on infections with *Plasmodium cathemerium* in ducks is described. Ducks aged 10 to 12 days and weighing 150 g. were infected by intravenous inoculation of a dose of 5×10^8 parasitized erythrocytes per kilo of body weight; the infection reaches its peak (30 to 50% of the erythrocytes infected) by the fourth day, and by the eighth day parasites are usually no longer visible in blood smears though subinoculation shows that they remain for months. The criteria of cure were: (1) no parasitological relapse after the end of treatment; (2) negative subinoculation; (3) an acute reinfection by a second inoculation of blood parasites 30 days after the first and 23 days after therapy. The experiments were made at the Squibb Institute for Medical Research and Rutgers University, New Brunswick, New Jersey.

Subinoculation and reinfection were more reliable tests than blood smears, but a few inconsistencies occurred with them, reinfection taking place when subinoculation caused infection and subinoculation failing to infect when reinfection failed. It was finally shown that reinfection together with pre-reinoculation smears forms a more reliable criterion than subinoculation. There were no spontaneous cures in 89 untreated controls.

Pamaquin and mepacrine were tested by giving them in the food; a diet level of 0·005% of pamaquine (equal to a daily drug intake of 15 mg. per kilo) cured 9 of 13 ducks and the ED 50 (the dose curing 50% of the ducks) was 17 mg. per kilo, while the ED 50 for suppressive activity was 1·2 mg. per kilo. Some deaths were due to drug toxicity, the curative doses being very near the toxic level. With mepacrine the ED 50 (curative) and the ED 50 (suppressive) were 95 mg. per kilo and 5 mg. per kilo respectively. Quinine bisulphate, in the highest doses that the ducks would accept in the food (0·085% diet level or 150 to 200 mg. per kilo quinine base), had no curative value; daily doses of 1,500 mg. per kilo given by stomach tube to 70 ducks cured none. The ratio of the ED 50 (curative) to the ED 50 (suppressive) of pamaquin was 14 and this could be used as a standard in the routine assay of curative drugs; the ratio for mepacrine was 19 and that for quinine, the least effective of the three drugs, was over 20. In such experiments some of the deaths, otherwise inexplicable, may be due to filtrable agents associated with the malarial infections used.

The authors conclude that a significant proportion of ducks infected with *P. cathemerium* can be cured with pamaquin or mepacrine but not with quinine.

J. F. Corson

2303. **Malaria. Observations on Treatment with Chloroquine (SN 7618) and Combined Quinine and Plasmochin**
T. A. WARTHIN, S. A. LEVINE, and R. R. EVANS. *New England Journal of Medicine* [*New Engl. J. Med.*] **238**, 467–469, April 1, 1948. 1 fig., 6 refs.

From July 1, 1946, to July 1, 1947, 125 cases of benign tertian malaria (*Plasmodium vivax*) of Pacific area origin were treated in the Veterans Administration Hospital, West Roxbury, Massachusetts. All the patients had had mepacrine in suppressive or therapeutic doses while in the Pacific area. In the hospital 26 received a 3-day course of chloroquine—1 g. and 0·5 g. after 8 hours on the first day, 0·5 g. on the second and third days—and most were discharged on the third day and told to take 0·5 g. weekly for 5 weeks; 103 patients were treated with plasmochin naphthoate (pamaquin), 0·02 g. every 8 hours for 14 days and quinine sulphate 1 g. every 8 hours on the first day and 0·6 g. every 8 hours for 13 days [see Most *et al.*, *Amer. J. med. Sci.*, 1946, **212**, 550, and *Abstracts of World Medicine*, 1947, **2**, 343].

Some patients (89) were followed up for 6 to 12 months, the rest [36?] for 1 to 6 months; among the 26 who received chloroquine the parasitic relapse rate was 42%

and the total rate was 84%, about equal to the rates after mepacrine treatment. No parasitic relapse occurred during 6 to 12 months among 63 patients treated with quinine and pamaquin, though 16 had some suggestive symptoms.

The authors conclude that chloroquine is as effective as mepacrine in acute relapses and is better tolerated, but has no greater effect on the relapse rate; the combined course of quinine and pamaquin markedly reduces the relapse rate, but to avoid toxic effects it should be given only to patients under observation and with restricted activity. *J. F. Corson*

2304. **A Study of the Prophylactic, Curative and Suppressive Activity of SN-11,437 (Metachloridine) in Standardized Infections of *Vivax* Malaria**

T. N. PULLMAN, A. S. ALVING, R. JONES, C. M. WHORTON, B. CRAIGE, and L. EICHELBERGER. *American Journal of Tropical Medicine* [*Amer. J. trop. Med.*] **28**, 413–423, May, 1948. 7 figs., 13 refs.

"Metachloridine", a proprietary name for N′-(5-chloro-2-pyrimidyl)metanilamide, was tried in benign tertian malaria because it has much greater prophylactic action in bird malaria than other sulphonamides. Its toxicity in laboratory animals is low, though very large doses cause hypoprothrombinaemia, haemorrhages, and other harmful effects. Volunteers, inmates of Illinois State Penitentiary, U.S.A., were infected with *Plasmodium vivax* (Chesson strain) by the bites of *Anopheles maculatus* and by inoculation of infected blood (Chesson and McCoy strains), and the prophylactic, curative, and suppressive activity of the drug was tested.

The drug is quickly absorbed when taken by mouth; 1·4 g. a day produced a plasma concentration of 11 mg. per 100 ml., but when sodium bicarbonate was also taken 4 g. daily of metachloridine was needed to give the same plasma concentration. Renal excretion of the drug was much increased when the urine was alkaline. A prolonged bleeding time in one man after large dosage was the only certain toxic effect. Volunteers received the drug 4-hourly on the day preceding the mosquito bites, on the day of the bites, and for 6 or 20 days afterwards; plasma concentrations were 10 to 14 mg. per 100 ml., and the total dosage varied from 44 g. to 82 g. Sodium bicarbonate was also taken to make the urine alkaline. Primary malaria was not prevented in any volunteer but the pre-patent period was lengthened by about the period of drug administration. Similar doses were used for treatment of primary infections and first and second relapses in sporozoite-induced infections; the drug was given alone in various doses and with sodium bicarbonate or with quinine, chloroquine, or pamaquin. It was about as effective as quinine, though parasites remained longer in the blood and relapses occurred after all the combinations, the relapse rate being not less than with other suppressive drugs. Metachloridine was tried alone and with alkali in both trophozoite-induced and sporozoite-induced infections; in the former it was given in divided doses by mouth for 4 days in a total dosage of 0·002 to 13 g. A total dosage of 1 g. or more resulted in cure; a total dose above 0·02 g. temporarily suppressed fever and parasitaemia. In the latter infections single weekly doses of 2 to 0·06 g. were given and repeatedly reduced until a dose was reached which failed to suppress the malaria (0·125 g. or less). There was complete suppression in 9 of 10 patients with weekly doses of 0·25 g. or more, but Coggeshall (personal communication) observed a 10% relapse rate with weekly doses of 1 g. *Plasmodium falciparum* is more resistant to this drug than *P. vivax*. *J. F. Corson*

2305. **A Comparison of the Effectiveness of Quinacrine and Quinine Against Falciparum Malaria**

J. MAIER, F. B. BANG, and N. G. HAIRSTON. *American Journal of Tropical Medicine* [*Amer. J. trop. Med.*] **28**, 401–406, May, 1948. 4 refs.

During the New Guinea campaign in the war of 1939–45 it was found that a course of 0·3 g. of quinacrine [mepacrine] daily for 5 days did not quickly control subtertian malaria, whereas the course given in the Australian Army of 2 g. of quinine hydrochloride daily for 3 days, then 0·4 g. of mepacrine daily for 5 days did so; symptoms often reappeared, however, in the early days of the latter mepacrine course because quinine had disappeared from the plasma on the fourth day and mepacrine had not yet reached an effective level in the plasma. This raised doubts about the efficiency of mepacrine which it was important to dispel; comparative observations were therefore made at the 2/7 Australian General Hospital.

Alternate soldiers admitted with subtertian malaria were treated with a standard course of mepacrine or quinine, each drug being given three times a day for 6 days. The daily doses of mepacrine were 1·2, 0·8, 0·4, 0·4, 0·4, 0·4 g., and those of quinine hydrochloride (in solution) were 2·6, 2·6, 2·6, 2, 2, 2 g.; slight modifications were made if urgently required. Temperatures were taken regularly and often the blood examinations included enumeration of parasites and estimations of plasma concentrations of mepacrine or quinine. There were 104 cases in the quinine series and 99 in the mepacrine series, and each series was subdivided into 3 groups, according to the density of infection on admission.

Plasma levels in the 3 groups were similar; mepacrine on the second day varied from 24 to 264 μg. per litre, only 1 reading being below the effective level of 30; while on the sixth day they varied from 15 to 179 μg. with only 1 under 30. Quinine on the second day varied from 4·4 to 14·8 mg. per litre, 2 readings being under the effective level of 5 mg.; while on the sixth day it varied from 1 to 11 mg.; with 37 under 5 mg.; 19 of the latter patients had 4 to 5 mg. In both series the temperature fell to normal within 48 hours in the lowest density group and within 72 hours in the other 2 groups. Gametocytes appeared in 13 of the patients receiving mepacrine and in 14 of those receiving quinine. Six of the patients taking mepacrine had brief nervous disturbances—acute mania in 4 and epileptiform convulsions in 2 with no history of epilepsy; such attacks were not seen in patients with benign tertian malaria given the same course of mepacrine; the plasma levels of mepacrine in the 6 patients were not abnormal.

Another series of 82 patients received mepacrine, 1·2 g. on the first day and 0·4 g. on each of the next 5 days (total 3·2 g.); this lower dosage produced adequate plasma levels. *J. F. Corson*

2306. **Metabolic and Haematological Disturbances in Malaria.** (Les troubles métaboliques et hématologiques dans le paludisme. Etude clinique, physiopathologique et thérapeutique)
I. RADVAN. *Annales de Médecine* [*Ann. Méd.*] **49**, 215–247, 1948. Bibliography.

ARTHROPODS

2307. **On the Venom of Scorpions *Prionurus australis* L. and *Prionurus aeneas* C. Koch.** (Sur le venin des scorpions *Prionurus australis* L. et *Prionurus aeneas* C. Koch)
E. SERGENT. *Archives de l'Institut Pasteur d'Algérie* [*Arch. Inst. Pasteur Algér.*] **26**, 21–24, March, 1948. 1 fig., 8 refs.

Eight species of scorpion are to be found in North Africa. The toxicity of their venoms varies very considerably and the following results were obtained for the minimal lethal dose for a mouse of 20 g. body weight of the dried and powdered telson. [The telson is the last segment from the body of a crustacean: in the case of a scorpion it contains the poison gland.]

Species	Minimum Lethal Dose
Prionurus australis L. ..	$\frac{1}{20}$ of a telson
P. amoreuxi Aud. ..	$\frac{1}{15}$,, ,,
P. hoggarensis Plry ..	$\frac{1}{12}$,, ,,
P. aeneas C. Koch ..	$\frac{1}{8}$,, ,,
Buthus occitanus Amx ..	$\frac{1}{2}$,, ,,
Hottentota gentili Plry ..	$\frac{1}{4}$ to 1 telson
Scorpio maurus L. ..	7 telsons

This table shows that, contrary to the popular view, large black scorpions are not the most dangerous, for the large black species are *P. hoggarensis*, *P. aeneas*, and *Hottentota gentili*. *G. M. Findlay*

FUNGUS INFECTIONS

2308. **Isolation of Pathogenic Fungi from Experimentally Inoculated Guinea Pigs**
A. HOWELL. *Public Health Reports* [*Publ. Hlth Rep., Wash.*] **63**, 602–616, May 7, 1948. 26 refs.

Guinea-pigs were inoculated intraperitoneally with *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Candida albicans*. They proved to be relatively resistant to infections with the first two, while none of those injected with *C. albicans* developed an infection. All but a few proved to be sensitized, the skin reactions being positive although they had been negative before inoculation. The organisms were occasionally isolated from the spleens of apparently healthy animals. *R. Salm*

2309. **Studies of Fungus Antigens. III. Sensitization of Normal Animals with Skin Test Antigens**
A. HOWELL. *Public Health Reports* [*Publ. Hlth Rep., Wash.*] **63**, 595–601, May 7, 1948. 8 refs.

The effects of simultaneous and repeated intradermal injections of 0·1 ml. of various dilutions of histoplasmin, blastomycin, an autoclaved filtrate of *Candida* (*Monilia*) *albicans*, heat-killed suspensions of the yeast-phase of *Histoplasma capsulatum* and *Blastomyces dermatitidis*, and of a 1–100 dilution of a heat-killed suspension of *C. albicans* on normal guinea-pigs have been studied. It has been shown that these antigens, if used in sufficient concentrations, may sensitize normal guinea-pigs.—[Author's summary.]

2310. **The Use of Coccidioidin**
C. E. SMITH, E. G. WHITING, E. E. BAKER, H. G. ROSENBERGER, R. R. BEARD, and M. T. SAITO. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **57**, 330–360, April, 1948. 2 figs., 61 refs.

A method is described for preparing coccidioidin in a medium containing *l*-asparagine, ammonium chloride, dipotassium phosphate, sodium citrate, magnesium sulphate, ferric citrate, dextrose, glycerin, and water, sterilized at 240° F. (115° C.) for 15 minutes. Strains do not differ much in their capacity to produce coccidioidin in this medium; no difference in potency is caused by grinding the mat or altering the conditions of filtration, but, as different batches vary in potency, coccidioidin batches should be standardized on man, non-reactors, reactors, and " equivocal " reactors being used.

Coccidioidin sensitivity is of " bacterial " type and is not transmissible passively. An immediate reaction (wheal with pseudopods developing in 15 minutes to 1 hour) or a delayed reaction developing in 6 to 24 hours, maximal at 36 to 48 hours and fading thereafter, may be observed. Sensitivity is developed in 2 days to 3 weeks after infection. Coccidioidal erythema nodosum reacts to coccidioidin, and in active infection coccidioidin testing may precipitate the development of erythema nodosum. In cases of generally disseminated coccidioidal granulomata there is usually reduced sensitivity to coccidioidin; if sensitivity to coccidioidin is maintained during dissemination the prognosis is better than if sensitivity falls. In most cases without dissemination, sensitivity falls very slowly; there seems little evidence that sensitivity is maintained by exposure to reinfection.

Coccidioidin is not antigenic and does not appear to sensitize man; sensitivity tests may therefore be carried out before serological examinations. The dosage is important, as severe reactions cause local discomfort and, occasionally, fever and general malaise; they do not, however, activate a quiescent infection, or cause general dissemination, or adversely affect an acute illness, except by precipitating erythema nodosum or erythema multiforme. Coccidioidin is very stable both to heat (it withstands 250° C. for 10 minutes) and to ageing—undiluted material is stable for at least 9 years, and, if uncontaminated, will keep diluted for many months.

No control is necessary if the asparagine synthetic medium is used for preparing coccidioidin. Great care is essential in the cleaning of syringes for injection of coccidioidin, because it is readily adsorbed on glass (like tuberculin) and cannot be destroyed by autoclaving. Syringes should, therefore, be new, or treated with acid dichromate solution overnight or boiled in it before use. Contamination of the coccidioidin, subcutaneous instead of intradermal injection, and inaccurate reading of reactions may invalidate the test. *C. L. Oakley*

2311. **Primary Pulmonary Coccidioidomycosis. Case of Laboratory Infection in England**
J. D. N. NABARRO. *Lancet* [*Lancet*] **1**, 982–984, June 26, 1948. 2 figs., 28 refs.

RHEUMATIC FEVER

2312. **The Toxic Manifestations of Sodium Salicylate Therapy**
J. D. P. GRAHAM and W. A. PARKER. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **17**, 153–163, April, 1948. 3 figs., 26 refs.

The authors gave sodium salicylate to 40 rheumatic patients and to 30 non-rheumatic convalescents; they studied toxic manifestations in relation to plasma salicylate levels. With progressively increasing levels the following were noted: erythema, tinnitus, deafness, nausea, vomiting, albuminuria, hyperventilation, marked sweating, headache, vertigo, severe drowsiness, acetonuria, haematuria, confusion, excitement, euphoria, pulmonary oedema, severe dyspnoea, and haemorrhage. The more serious signs were noted with a salicylate level of more than 35 mg. per 100 ml.

The authors describe human and animal experiments, from which they conclude that vomiting due to salicylate is of central origin; that hyperpnoea is directly caused by salicylate; that the fall of carbon-dioxide combining power is a secondary effect; and that the vagal endings are the sites of stimulation for the hyperpnoeic effect. [The evidence for this last conclusion is unsatisfactory. We are not informed which of the manifestations arose in rheumatic patients and which in controls. It is therefore not possible to conclude which were indeed due to salicylate and which were not, especially since many of them might have arisen in untreated rheumatic fever. It is also essential to know whether or not the patient with pulmonary oedema had been given salicylate in intravenous fluid.] *G. Loewi*

2313. **Does Sodium Salicylate Cure Rheumatic Fever?**
J. REID. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **17**, 139–151, April, 1948. 5 figs., 6 refs.

To answer the question contained in the title the author studied 12 patients; 9 adults had polyarthritis, fever, and tachycardia; 3 children had pericarditis, fever, and tachycardia. Sodium salicylate was given by mouth: 7 adults received 2 g. of sodium salicylate and 2 g. of sodium bicarbonate 5 times each day; 2 adults received 10 g. of sodium salicylate a day only; 2 children were given 1·3 g. sodium salicylate and 1·3 g. sodium bicarbonate 5 times a day, and 1 child sodium salicylate only. Venous blood and the total urinary output were collected daily for salicylate estimations.

Plasma salicylate levels of 20 to 46 mg. per 100 ml. were reached in 3 to 8 days, then a fall occurred. Higher levels were reached and maintained without added sodium bicarbonate, probably due to less urinary excretion. At the highest plasma salicylate levels there was depression of alkali reserve and urine *p*H. The author concludes that the rate of disappearance of pain, fever, and tachycardia and the rate of fall in the erythrocyte sedimentation rate are proportional to the height of the plasma salicylate level. In one case it is even claimed that pericardial friction disappeared and reappeared with rise and fall respectively in salicylate level. [No electrocardiographic evidence of pericarditis is offered, and since the patient was febrile when friction was heard it is conceivable that this was due to a dilated pulmonary artery as suggested by Ortiz (*Arch. lat.-amer. Cardiol. Haematol.*, 1933, **3**, 45).] The author thinks that plasma salicylate levels should be kept between 30 and 40 mg. per 100 ml. while disease is active. *G. Loewi*

2314. **Rheumatic Fever: *p*-Aminobenzoic Acid.** (Fièvre rhumatismale: acide para-aminobenzoique)
M. BÉLISLE. *Union Médicale du Canada* [*Un. méd. Can.*] **77**, 392–425, April, 1948. 5 figs., 233 refs.

A report on some observations on the effect of *para*-aminobenzoic acid on the salicylate level of the blood during sodium salicylate therapy is preceded by a review of the aetiology, symptomatology, diagnosis, and treatment of rheumatic fever. This review includes a summary of the recent evidence of the possible anaphylactic nature of the lesions; of the possible role of hyaluronidase —the "spreading factor", which increases the permeability of the vessels in infective processes; and of observations demonstrating the value of sulphonamides in prophylaxis.

para-Aminobenzoic acid, possibly a part of the vitamin-B complex, is a non-toxic substance which plays an essential part in syntheses necessary for bacterial growth; it inhibits the bacteriostatic action of sulphonamides and the growth of rickettsia, and has been used with excellent results in typhus. It was reported in 1946 that if *para*-aminobenzoic acid were administered by mouth to patients undergoing sodium salicylate therapy, a rise in the salicylate level of the blood was provoked. Three cases are now reported in which this observation is confirmed. The patients received 24 g. of *para*-aminobenzoic acid daily, divided into 2-hourly doses. The salicylate level of the blood was found to be increased up to 2 to 5 times its initial level. With relatively small doses of sodium salicylate it is possible in this way to obtain a blood concentration of 35 mg. per 100 ml., which is considered the optimum in the treatment of rheumatic fever. It may have a place in therapeutics when the necessary blood concentration cannot be obtained by the administration of salicylate alone, but its limitation is the need for 2-hourly doses because it is rapidly eliminated. *Kenneth Stone*

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ASSISTED BY

S. S. B. GILDER, B.Sc., M.B., B.S.

This journal is planned to provide the reader with a selection of abstracts of the more important articles appearing in medical periodicals published in different parts of the world. Comment by the abstracter, when thought necessary, is inserted between square brackets, usually at the end of an abstract. In some instances only the titles of articles are provided.

After the title of each journal from which an abstract is taken we print the abbreviation given in the *World List of Scientific Periodicals*. The titles of articles from foreign journals are translated into English.

This journal is essentially a guide to work in progress in the world's medical centres. No abstract can be regarded as a substitute for the article abstracted. For complete information the original article must be consulted. Our aim is to give the reader sufficient details in an abstract to enable him to judge whether the original is, for him, worth reading in full.

The abstracts are grouped in broad classifications which represent the special fields of study into which Medicine is divided. The specialist will, it is hoped, learn in this journal of work done in other fields as well as in his own. The general practitioner will be able to keep abreast of modern knowledge in the various specialties. The representation in one journal of the several aspects of Medicine will, it is believed, give an integrated picture of the whole, necessary in this age of specialization.